

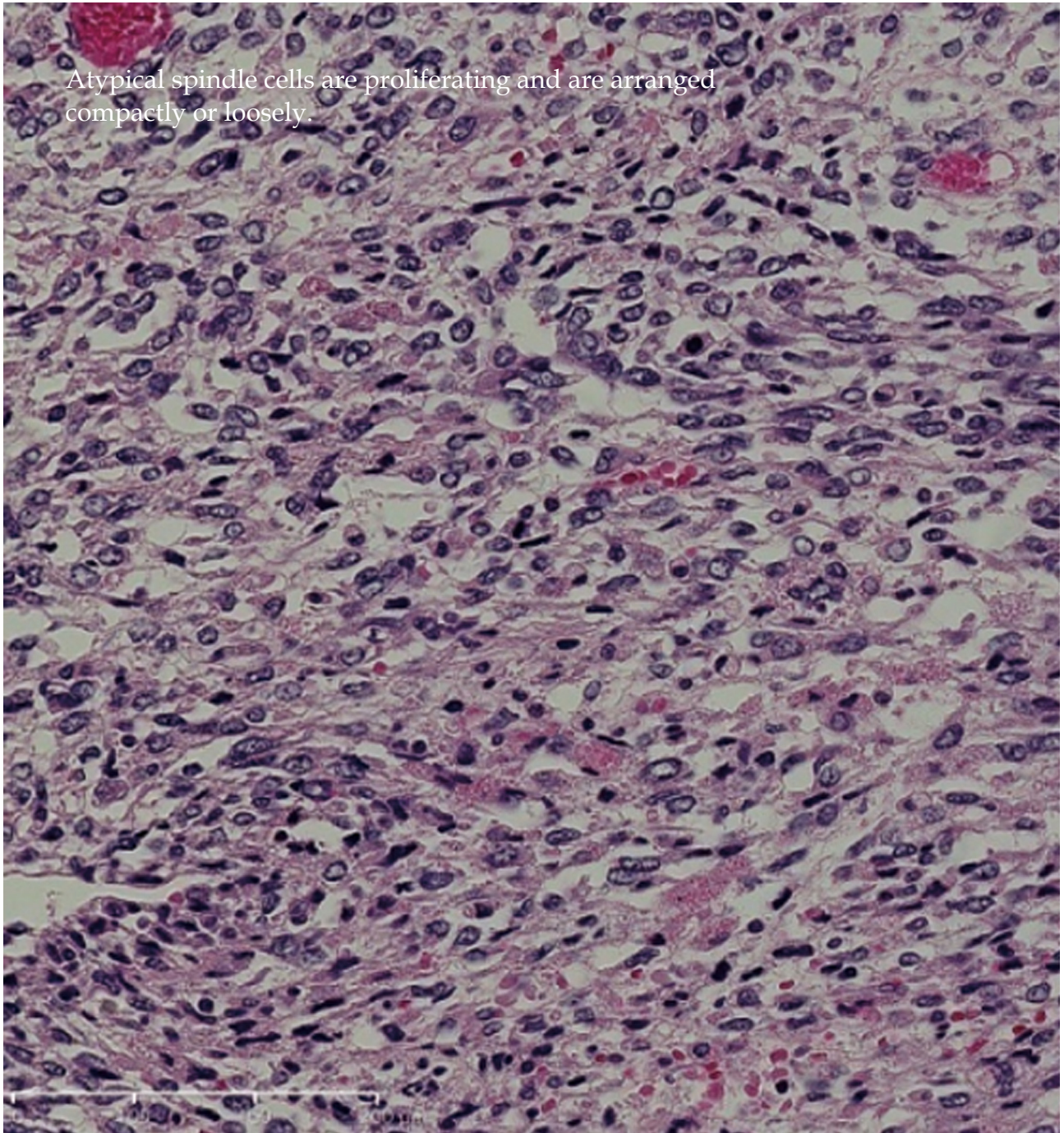


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Positron emission tomography as predictor of rectal cancer response during or following neoadjuvant chemoradiation

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Abstract

Positron emission tomography (PET) shows great promise as a tool to evaluate the effectiveness of rectal cancer neoadjuvant therapy as it has demonstrated high predictive value in several studies. Creating a standardized method of using PET has the potential to reduce ineffective treatments. However, relevant studies have been heterogeneous in approach, making any unified standard difficult to establish. PET related parameters used to assess treatment response include magnitude and change of standard uptake value, total lesion glycolysis, and visual response. Finding the best evaluation interval and parameters to use for interpreting PET results in the neoadjuvant treatment of rectal cancer needs additional study.

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Key words: Positron emission tomography; Rectal cancer; Neoadjuvant therapy

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Colorectal cancer was the third most common cancer in 2009 with 75 590 new cases in men and 71 380 new cases in women in the U.S. in spite of the fact that its incidence has been decreasing over recent years. It is also the second leading cause of cancer deaths in United States, and survival at 5 years is around 66%^[1]. New chemotherapeutics and improved screening (earlier detection) have contributed to the improving outcomes and survival^[2]. With improved detection and treatment, the presence and change of metabolic characteristics prior to, during, and subsequent to local and systemic therapy is of increasing importance in assessing disease status and making management decisions. For this reason, 18F-deoxyglucose (FDG) positron emission tomography (PET) imaging is increasingly used in the staging and management of colorectal cancers.

PET imaging holds great potential value as a diagnostic and management tool. Unfortunately, PET imaging has limitations in terms of image resolution and image noise created by non-malignant metabolic processes such as treatment-related inflammation. While a number of studies support the idea that PET imaging can be predictive of chemoradiation treatment response, the timing of PET imaging as well as the specific image parameters used for interpretation widely differ in the literature. Here we will examine these issues to review PET's role in the clinical management of colorectal cancer, particularly in relation to preoperative radiotherapy and multimodality therapy response evaluation.

The RECIST criteria (response evaluation criteria in solid tumors) have been widely used to characterize tumor response to therapy^[3]. These criteria are based on tumor

size change; specifically, tumor response is designated as a decrease in the sum of the largest diameters of target tumor lesions of at least 30%. However, viability of tumor tissues and cellular reproductive integrity are not necessarily associated with changes in tumor size, and the correlation between size response and patient outcome has been shown to be weak. For example, angiogenesis inhibitors may change the micro-environment of the tumor in a manner that does not immediately or dramatically change size, but effectively decreases tumor viability. In such a case, a metabolic imaging tool such as PET may help in early response assessment where other assessment tools may be inadequate. This may prevent additional futile therapy or allow for a timely change to an alternative therapy.

PET is most valuable when interpreted with morphologic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound. PET scans are frequently obtained with a registered CT scan; in this way, both imaging sets can be obtained with the patient in the same position, and image registration makes the combined functional and morphological information of the scans more readily apparent. However, CT scans are obtained within a shorter time period than PET scans, and registration accuracy may suffer^[4]. The longer period of image acquisition associated with PET is partly responsible for the modality's lower resolution with time-averaging of normal internal organ motion.

PET's utility in colorectal cancer has already been demonstrated in a number of ways. Pre-hepatectomy assessment is better performed and residual masses are well identified with PET imaging. PET is useful for localizing recurrences in patients with an unexpected rise in carcinoembryonic antigen levels after surgery^[5]. There is some indication that therapy can be tailored to patients with PET-based stratification. However, appropriate usage of PET for post-treatment evaluation of neoadjuvant chemotherapy or radiation is still being defined. A number of studies demonstrate that the modality holds promise, although there is nothing that would constitute a clear foundational guideline for PET application to clinical decision making in that setting.

Perhaps one reason a unified guideline for PET interpretation has not been created is that the quantitative analysis of PET imaging can vary widely, with several markers such as standardized uptake value (SUV) max, SUV mean, dTLG (total lesion glycolysis), metabolism rate of glucose, visual response, *etc.* as possible candidates for interpretational dividers. Each discrete marker can also be compared between sequential scans, adding additional parameters that may be best for interpretation. Uptake values are by their nature relative values and depend on the manner of administering the test. Attenuation and other correction factors are applied to account for institution-specific equipment and circumstances, and this prevents direct comparisons to imaging from other institutions. Because of the nature of correction algorithms, SUV and other values are not fully amenable to absolute comparisons between

and within institutions. Additionally, patient metabolism and health history also affect the uptake and vary depending on the circumstances of an individual test's administration.

With the exception of very early tumors that can be managed with local excision, rectal cancers are managed with radical surgery. Despite improvements in surgical technique with total mesorectal excision, local recurrence rates justify multimodality therapy in appropriate patients^[6]. Preoperative chemoradiation improves the local control rate, but distinguishing responders from nonresponders can be difficult prior to the post-operative histopathological analysis. However, accurate restaging prior to surgery is important to help determine the optimal surgical strategy. For example, extent, aggressiveness, and sphincter preservation may all be considered in light of the treatment response. Response assessment during neoadjuvant chemoradiation can also allow for tailored therapy using alternative dosing, fractionation, or agents. Because anatomic imaging modalities can't accurately distinguish between viable and non-viable tissue, the functional approach provided by PET imaging is conceptually an appealing alternative.

In a 1992 report on PET's utility in response assessment, Engenhardt *et al*^[7] reported a significant small decrease in the SUV of tumor following irradiation of nonresectable pre-sacral recurrent rectal carcinomas and suggested that enhanced glucose uptake is associated with recurrent rectal cancer. Conclusions from the report were conservative stating that the characteristics of normal physiological uptake (including proliferation, repair, and inflammation) needed to be further characterized before PET could reliably distinguish them from residual viable tumor and therefore be useful for radiation treatment monitoring. Table 1 summarizes key studies in evaluating rectal cancer treatment response.

Further work has approached response assessment by evaluating other imaging related parameters with mixed results. Siegel *et al*^[8] reported that a significant 40% reduction in SUVmax was observed with PET 17 d after starting radiation for locally advanced rectal cancer, but with no correlation between SUVmax reduction and downstaging or other markers. They did conclude, however, that PET can monitor early effects of short course radiotherapy using post-treatment SUVmax as a surrogate marker for treatment response. Similarly, Oku *et al*^[9] used post treatment SUV values as a predictive marker, but in this case of long-term prognosis. They found that neither pre-therapy SUV nor the ratio of post and pre-treatment SUVs had prognostic usefulness. There was a significant difference in recurrence correlated with post-therapy SUVmean. Nakagawa *et al*^[10] demonstrated a significant survival benefit in patients with low uptake after preoperative radiotherapy in primary tumors of rectal cancer.

Apart from uptake quantification, visual response has also been tested as a predictive marker. Guillem *et al*^[11] prospectively studied several parameters in 21 patients receiving pre-operative chemoradiation, including SUVmean,

Table 1 Relevant studies of PET in evaluating rectal cancer treatment response

Study	n	Therapy	Timing	Response criteria	Outcome measure	Result	P
Engenhart <i>et al</i> ^[7] (1992)	21	RT	8-9 wk pc	ΔSUV	LC	SUV normalization; PPV 20%; NPV 67%	
Schiepers <i>et al</i> ^[14] (1999)	9	RT	2-3 wk pc	TuGluc	Histo, cell kinetics	Decreased 138 nmol/mL per min after RT	0.008
Guillem <i>et al</i> ^[11] (2000)	15	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Histo	VR PPV 60%	
Oku <i>et al</i> ^[9] (2002)	40	RT	3-5 wk pc	SUV	Recurrence	SUV < 3.2	< 0.05
Amthauer <i>et al</i> ^[15] (2004)	20	CRT + H	2-4 wk pc	ΔSUV	Histo	36% decrease SUV PPV 93%; NPV 100%	0.003
Calvo <i>et al</i> ^[16] (2004)	25	CRT	4-5 wk pc	ΔSUV	Histo	2 vs 2.7 decrease SUV	NS
Guillem <i>et al</i> ^[17] (2004)	15	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Recurrence, OS, RFS	63% decrease SUV 70% decrease TLG	0.08 0.03
Denecke <i>et al</i> ^[18] (2005)	23	CRT + H	2-4 wk pc	ΔSUV	Histo	36% decrease SUV PPV 77%; NPV 100%	0.002
Konski <i>et al</i> ^[19] (2005)	20	CRT	3-4 wk pc	ΔSUV	Histo	52% vs 75% decrease SUV	NS
Cascini <i>et al</i> ^[20] (2006)	33	CRT	12 d pi	ΔSUV	Histo	22% vs 63% decrease SUV	< 0.0001
Capirci <i>et al</i> ^[13] (2006)	88	CRT	5-6 wk pc	Negative PET	5 yr OS and DFS	91% vs 72% 81% vs 62%	0.024 0.003
Kalff <i>et al</i> ^[12] (2006)	34	CRT	7-43 d pc	VR	OS PFS	100% vs 79% 100% vs 47%	< 0.0001 < 0.0001
Capirci <i>et al</i> ^[21] (2007)	45	CRT	5-6 wk pc	ΔSUV	Histo	66% decrease SUV PPV 77%; NPV 89%	0.0015
Melton <i>et al</i> ^[22] (2007)	21	CRT	4-5 wk pc	ΔSUV, VR, δTLG	Histo	70% decrease SUV PPV 58%; NPV 100%	< 0.001
Kristiansen <i>et al</i> ^[23] (2008)	30	CRT	7 wk pc	VR	Histo	PPV 83%; NPV 33%	NS
Siegel <i>et al</i> ^[8] (2008)	32	RT (short)	7-8 d pi	ΔSUV	Histo	40% decrease SUV	NS
Nakagawa <i>et al</i> ^[10] (2008)	59	RT	2-3 wk pc	SUV	OS MS	SUV < 5: 95 vs 42 mo, 70% vs 44%	0.042
Vliegen <i>et al</i> ^[24] (2008)	20	CRT	4-6 wk pc	ΔSUV	Histo	83% vs 59% decrease SUV	0.025
Janssen <i>et al</i> ^[25] (2009)	30	CRT	2 wk pc	ΔSUV	Histo	43% decrease SUV PPV 91%; NPV 82%	
Konski <i>et al</i> ^[26] (2009)	53	CRT	3-4 wk pc	ΔSUV	Histo	67% vs 55% decrease SUV	NS
Rosenberg <i>et al</i> ^[27] (2009)	30	CRT	pc	ΔSUV	Histo	66% vs 48% decrease SUV PPV 83%; NPV 64%	0.040

PET: Positron emission tomography; RT: Radiation; CRT: Chemoradiation; CRT + H: Chemoradiation with hyperthermia; pc: Post completion; pi: Post induction; δTLG: Change in total lesion glycolysis; TuGluc: Tumor glucose utilization; VR: Visual response; Histo: Histopathology; LC: Local control; OS: Overall survival; MS: Median survival.

SUVmax, PET-derived tumor size, visual response score, and change in total lesion glycolysis. Visual response score showed the most potential, accurately estimating the extent of pathologic response in 60% of cases compared with 22% of cases with CT^[11]. Kalff *et al*^[12] graded tumor response as complete, partial, or absent, based on visual assessment. At median follow-up of 3.1 years, all 17 patients with a complete visual metabolic response continued free of disease while 6 of the 10 patients with a partial visual metabolic response were disease free and all 3 nonresponders had died.

In a larger study, Capirci *et al*^[13] performed PET on 88 patients 6 wk after the completion of chemoradiation, to assess response. Surgery was performed between 8 and 9 wk after completion of chemoradiation. With a median follow-up after surgery of 38 mo, overall survival was 91% in patients with negative post-treatment PET and 72% in those with a positive PET ($P = 0.024$). Disease-free survival was 81% in patients with negative PET and 62% in those with positive findings ($P = 0.003$). Negative PET was defined as "faint and diffuse uptake" while positive PET was defined as "intense, moderate, or mild focal or

diffuse uptake" as determined by visual inspection.

While collectively there is fairly persuasive evidence that PET can successfully indicate clinical response, a review of the literature provides little guidance on how precisely to use PET-derived response information. Retrospective data have shown stronger relationships between PET values and response, although these associations have not been strong in prospective studies. Specific SUVmax or SUVmean cutoff values vary between reports and have been determined retrospectively, tailored to the study population. There has also been a change in the technical format of PET delivery as centers switch to PET/CT machines to improve imaging registration. The change to PET/CT has been accompanied by a change in the attenuation correction algorithms used for PET image production, and this may have caused a shift in the magnitude of PET parameters. Finally, normal tissue uptake can be confusing within the pelvis as bowel lumen, uterine cavity or muscular uptake provide increased noise.

Overall, PET shows great promise as a tool to evaluate the effectiveness of rectal cancer neoadjuvant therapy as it has demonstrated high predictive value in several studies.

However, it is important to note that PET cannot be considered as surrogate for complete pathological response because patients with complete PET response often harbor residual microscopic disease. Therefore, appropriate surgical resection should be done even in patients with a complete PET response. Finding the best evaluation interval and parameters to use for interpreting PET results needs additional study. Creating a standardized method of using PET has the potential to reduce ineffective treatments when patients are not responding as well as modify surgical planning to decrease morbidity for those patients who are.

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Tumor stem cell, or its niche, which plays a primary role in tumorigenesis?

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Abstract

Cancer research over the past decades has focused on neoplastic cells, or a fraction of them, i.e. tumor stem cells, as the ultimate causes of tumorigenesis. However, during recent years, scientists have come to realize that tumorigenesis is not a solo act of neoplastic cells, but rather a cooperative process in which the roles of numerous types of non-neoplastic cells should be recognized. These tumor-residing non-neoplastic cells constitute the so-called tumor-associated stroma, which in certain cases even greatly surpasses the neoplastic cellular compartment that was previously thought of as a sole determiner leading to a seemingly autonomous growth pattern. In this review, we summarize several recent research highlights that have unveiled many previously unappreciated roles for microenvironmental factors, especially during the initiation stage of tumorigenesis. It is becoming increasingly clear that the stroma's regulatory effects constitute not only an essential force for maintaining tumor growth, but also primary causes initiating tumorigenesis.

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Key words: Tumor stem cells; Stroma; Tumorigenesis; Initiation; Maintenance

INTRODUCTION

In spite of the fact that tumor-caused mortality rates have actually declined by about 10%-18% over the last decade, tumors are still among the leading causes of human mortality ranging from middle to old age. This situation, to a great extent, reflects a looming fact: the cellular and molecular bases underlying tumor origin and development still remain largely obscure to our comprehension.

From the viewpoint of mainstream medical research, tumorigenesis is basically a process of neoplastic cell autonomy wherein a few genetic or epigenetic alterations intrinsically occurring to a given somatic cell (presumably a somatic stem cell or progenitor) transform it into a tumorigenic cell, which, in turn, will embark on an out-of-control growth, successfully defying the regulatory activities from surrounding normal tissue cells, such as contact inhibition and immunosurveillance from the immune system. Nevertheless, even as early as several decades ago, occasional scientific reports emerged indicating that, at least for certain types of neoplasia, the tumorigenic growth is not such a totally autonomous process but needs cooperative actions from certain environmental factors. Notably, around

the turn of this century, this unorthodox thought has gradually come into the spotlight. Accumulating works have since revealed that the versatile roles of tumor stroma, to different extents, contribute to the development and clinical manifestation of neoplasia. In the following sections, we will propose several representative scenarios, emphasizing the plausible primary contributions of tumor-associated stroma to the initiation of tumorigenesis.

PRIMARY FACTORS OR DEFECTS DERIVED FROM STROMA MAKE NECESSARY CONTRIBUTIONS TO MALIGNANT TRANSFORMATION

The primary roles of intrinsic defects within neoplastic cells for initiating tumor formation have long been established. Accordingly, it is easy to accept the notion that neoplastic cells will exert potent stimulatory effects to coax stroma into a supportive microenvironment for the sake of their growth. It was probably hard to envision decades ago that certain primary factors or defects within the stroma might constitute a permissive role or an essential fueling force to drive the malignant transformation. As illustrated in the case of AKT activation-driven anchorage-independent growth of melanocytes and their malignant transformation, a hypoxic environment of normal skin plays a permissive role *via* stimulating HIF1 α activity^[1]. Conversely, a normoxic environment will greatly inhibit HIF1 α activity and, thus, inhibit the occurrence of melanoma even in the presence of oncogene activation. Subsequent studies suggested that tumorigenesis regulatory mechanisms may involve: (1) normoxia will decrease HIF1 α activity, allowing an expression of α integrin 5 that, in turn, will prompt anoikis of pre-tumor stem cells (TSCs) of melanoma during the tumor budding stage; (2) HIF1 α activation increases mRNA and protein levels of Notch1, which facilitates melanoma development even in xenograft models; and (3) HIF1 α activates the expression of macrophage migration inhibitory factor to delay premature senescence.

In another study, a common genetic effect occurring in both focal neoplastic cells and stromal mast cells was shown to elaborate tumor formation of the neurofibroma, which is notably composed of multiple types of tissue cells including Schwann cells, fibroblasts, endothelial cells, hematopoietic cells and pericytes/smooth muscle cells. It was previously observed that the loss of heterogeneity of tumor suppressor gene neurofibromatosis type 1 (*Nf1*) in Schwann cells is necessary, but not sufficient, to fuel the tumor formation. On the other hand, during neurofibroma formation in the *Nf1*-deficient mouse model, it was noticed that an infiltration and/or expansion of c-Kit⁺Fc ϵ RI⁺ mast cells into peripheral nerves preceded the manifestation of clinical tumors^[2]. Remarkably, hematopoietic cells, of which the majority are actually mast cells, account for 3%-7% of tumor cellularity. Yang *et al.*^[2] elegantly demonstrated that a haploinsufficiency of *Nf1* within hematopoietic mast cells is absolutely required for *in vivo* mast cell infiltration as well as the tumor formation that is otherwise characteristic of

the proliferative *Nf1*^{-/-} Schwann cells. To further support an essential contribution from the mast cells, the mast cells with a genetic defect in the *c-Kit* gene or wild type mast cells with a prior inhibition on c-Kit kinase activity, failed to support the tumorigenic proliferation of *Nf1*^{-/-} Schwann cells. Actually this study poses an exceptional case wherein tumor formation may not always arise from the primary defects within a single cell as the tumor clonal theory has claimed, and that the primary defects within two lineages of cells might be needed for the initiation and development of tumors.

PRIMARY ABNORMALITIES IN STROMA STIMULATE A NEOPLASIA-LIKE PHENOTYPE WITHOUT MALIGNANT TRANSFORMATION

What about the situations wherein the primary defects occur only in stroma cells? Can a neoplasm arise that is mainly composed of non-stromal cells with a normal genetic background? Two elegant works by Walkley *et al.*^[3] and Kim *et al.*^[4] have actually illustrated this out-of-expectation scenario. The first study involved the development of myeloproliferative disorders (MPD) that featured a phenotype of granulocytosis, which have been largely regarded as a group of neoplasia intrinsic to hematopoietic stem cell (HSC) defects (such as in the case of JunB deficiency of HSCs). Intriguingly, Walkley *et al.*^[3] have revealed a deficient hematopoietic microenvironment component that is sufficient to result in the development of a full scale MPD phenotype in mouse models. Although the exact cellular and molecular mechanisms are still awaiting further clarification, the reciprocal bone marrow transplantations between *RAR γ* ^{+/+} and *RAR γ* ^{-/-} strains have clearly pinpointed a retinoic acid signaling defect within the hematopoietic microenvironment, but not in the HSCs, as the primary cause of this special subtype of MPD. Notably, neither *RAR γ* ^{+/+} nor *RAR γ* ^{-/-} hematopoietic cells within a *RAR γ* ^{-/-} microenvironment were malignantly transformed by acquiring proliferative autonomy. In support of this scenario, in a likely case, a primary defective Notch activation arising from *Mib1* deficiency within a microenvironmental compartment, but not within hematopoietic cells, also caused a MPD-like phenotype^[4].

This scenario of a primary stromal defect-fueled abnormal proliferation of non-stromal cells is not only restricted to liquid neoplasia. As revealed in a study of the smooth muscle cell-targeted *Lkb*^{+/+} or *Lkb*^{-/-} mouse models, Katajisto *et al.*^[5] observed that the occurrence of Peutz-Jeghers syndrome, an abnormal epithelial proliferation along the gastrointestinal tract that is at high risk of forming carcinoma, was attributed to a featured increase of Sma⁺Desmin⁻ myofibroblast component within the stromal area of gastrointestinal polyps. The myofibroblast-like cells cored the polyps, and a reduced Smad-2 phosphorylation level was evident within the epithelial cells of the proliferative zone, especially within those surrounding

the Sma⁺ fibroblast-like cells, indicating that a molecular mechanism relating to a decreased production of TGFβ by *Lkb¹-* stroma was responsible for the abnormal epithelial proliferation.

PRIMARY ABNORMALITIES IN STROMA COAX AN OSTENSIBLY NORMAL CELL INTO REAL TSC

Further, it is interesting to ask whether a primary stromal defect can serve as the ultimate cause underlying the malignant transformation of non-stromal compartments. The answer probably is yes. Indeed in certain circumstances, the abnormal microenvironment can serve as a potent carcinogen, as illustrated in studies of the enhanced activities of stroma-derived metalloprotease-3 and -9 (MMP3 and MMP9)^[6]. Abnormally elevated activity of MMPs was found to deplete the surface E-cadherin of mammary cells, which led to the loss of cell-cell adhesion, relocalization of β-catenin into the nucleus, expression of Rac1b isoform, and the generation of reactive oxygen species^[6]. Finally, the resulting epithelial-mesenchymal transition and genomic instability fueled the development of overt breast cancer at a high frequency.

As mentioned above, it is well demonstrated that deficiency of TGFβ signaling in epithelial cells leads to their malignant transformation. On the other hand, recent work by Kim *et al*^[7] indicated an unexpected scenario in which a primary TGFβ signaling defect within T lymphocytes, but not within the epithelium, triggered the generation of a familial juvenile polyps-like syndrome that spontaneously evolved to metastatic gastrointestinal cancer. In the analyses of two T helper lymphocyte-restricted conditional *Smad 4^{-/-}* mouse models^[7], the authors discovered that a prominent infiltration of IgA-secreting plasma cells occurred to the epithelial neoplasm microenvironment, which indicated a skewed production of Th2 type cytokines including IL-6 by *Smad 4^{-/-}* T lymphocytes. In this regard, strong evidence from both human and murine studies is available, revealing a common transforming mechanism that consistent IL-6 signaling through Stat3 activation is associated with malignant transformation of gastrointestinal tract epithelium^[8,9].

A PARACRINE MODEL OF TSC OR PRE-TSC-DERIVED SIGNALS TO ACTIVATE OR EVEN SELECT THE OUTGROWTH OF ABNORMAL STROMAL CELLS

On the other hand, probably in most cases, we need to accept the notion that malignant neoplastic cells do predominate in the origin and progression of tumor tissues. However, even in these situations, the oncogenic activity of a primary defect within neoplastic cells has to be realized *via* a mediating role of the otherwise normal stromal cells. This scenario is well demonstrated in understanding the

oncogenic roles of an active Hedgehog (Hh) signaling status detected in many types of tumors. Numerous previous studies have indicated an autocrine mode of Hh for prompting the growth of neoplastic cells. However, in a recent analysis concerning the development of epithelial tumors^[10], it was discovered that some previous reports that presumed an inhibiting effect of Hh inhibitors on *in vitro* epithelial tumor growth *via* an autocrine mechanism of Hh signaling, actually came from “off-target” activity. In line with this, it was shown that an epithelium-specific transgenic expression of Smo^{m2} itself, an active mutant of Smoothened, failed to induce the malignant transformation of pancreatic cells. Based on the analyses of human primary tumor samples-nude mouse xenograft models, Yauch *et al*^[10] further demonstrated a relationship between the expression levels of *IHh* and *SHh* in inoculated tumor cells with those of *Gli* and *Patch* in host-derived stroma, while at least within some successfully implanted tumor samples, no evidence for Hh signaling activation within neoplastic cells themselves was confirmed. As expected, in these xenograft models, the administration of Hh signaling inhibitor or Hh-neutralizing antibody indeed delayed the growth of tumor, and the MEF cells from wild type, but not from a *Smo^{-/-}* background, were found to support the inoculation and growth of primary tumor cells expressing Hh, indicating a critical role for an Hh paracrine mechanism from tumor to stroma. The stroma would supposedly send feedback to neoplastic cells after Hh signaling activation, constituting an essential force fueling the tumorigenesis of the epithelium.

Finally, it must be emphasized that, in certain circumstances, some detectable genetic or epigenetic abnormalities in stroma cells represent a secondary response to malignant tumor cell-derived stimuli or even stress, rather than a primary event. In a murine prostate cancer model, as generated by the epithelial transgenic expression of *Apt121*, a potent Rb pathway inactivator, it was observed that tumorigenic progression was dependent on the genetic status of *p53* within stroma; i.e. wild type, heterozygous or null^[11]. The *TgAPT121* prostate tumor with a *p53^{-/-}* background has been characterized as having an extensive hypercellular mesenchyme, even with a so-called stromal tumor. The phenotypic characterization of Sma⁺S100A4⁺CK8⁻ fibroblast-like stroma indicated that it was not derived from a feasible epithelial to mesenchymal cell trans-differentiation. Most intriguingly, the proliferative mesenchyme within prostate cancer with a *p53^{+/+}* and *p53^{+/-}* background was found to experience a progressive loss of *p53* copies, indicating the stress-response of stroma to prostate cancer selectively favors the out-growth of the abnormal stroma with defective *p53* function.

CONCLUSION

Do tumors develop independent of tumor microenvironment-derived supporting cues? Now the answer is clear. The tumor microenvironment exerts a tremendous effect on tumor budding and progression; and sometimes the altered stroma even constitutes the sole ultimate cause fueling the tumorigenesis. The interplay between the

microenvironment and the evolving tumor cells is dynamic and complex, involving extensive reciprocal interactions. Changes in the context in which a tumor is hatching will largely determine the tipping of the balance either in favor of desirable tumor-suppression or undesirable tumor-promotion. Worthy of mentioning, these new findings convey at least two important biological implications: (1) for clinical tumors that need an essential contribution from certain primary defects of nonneoplastic stroma to originate and develop, the conventional method of measuring TSCs, based on the conventional conception of the clonal nature of tumorigenesis, may fail by simply inoculating a sole neoplastic compartment of tumor tissues into normal syngeneic or several routinely used immunocompromised recipients, such as NOD/SCID mice; and (2) perhaps for all types of clinical tumors, the interplay pathways between tumor cells and non-neoplastic stroma represent new avenues open to influence by therapeutic interventions. Therefore, understanding and developing accurate strategies aimed at cancer-supportive or tumor-inductive microenvironments, in combination with the standard anti-tumor approaches, seems to be most promising for preventing the development of or eradicating well-established tumors. Results from researches on these approaches are anticipated.

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New progress in CT and MRI examination and diagnosis of small intestinal tumors

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recent progress in imaging (CT and MRI) examination and diagnosis of small intestinal tumors.

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Abstract

Precise examination and diagnosis of small intestinal tumors is difficult because of the curved course and overlapping canal of the small intestine. Traditional technology for intestinal canal examination and endoscopy cannot exhibit the intestinal wall and extra-luminal structure well. With the development and advancement of multi-slice spiral computed tomography and magnetic resonance imaging (MRI), computed tomography enteroclysis (CTE) and magnetic resonance enteroclysis (MRE) are widely used in the examination and diagnosis of small intestinal tumors. CTE and MRE, with three-dimensional imaging capabilities and excellent soft-tissue contrast, can analyze the abnormalities of peripheral intestinal structure as well as the tunica mucosa. In addition, these two technologies can clearly reveal the localization, appearance, degree of mesenteric infiltration and remote tumor metastasis, which increases our cognition of the imaging diagnosis for intestinal tumors. Here we review

INTRODUCTION

The small intestine is the longest part of the digestive tract accounting for 75% of the total length of the digestive tract. The small intestine is not a common site for the development of neoplasm, accounting for only 1%-3% of all primary gastrointestinal tumors^[1,2]. Malignant tumors are mainly located in the ends of the small intestine; i.e. the ileum and duodenum^[3], accounting for approximately 3% of gastrointestinal malignant tumors. Clinical diagnosis of small intestinal tumors is difficult due to the lack of typical clinical symptoms and effective approaches for inspection in the past. With the rapid development of techniques in endoscope and medical imaging, especially the application of multi-slice spiral computed tomography (MSCT) and magnetic resonance imaging (MRI) in small intestine, both detection and diagnosis of small intestinal tumors has improved significantly.

MSCT/MRI EXAMINATION OF SMALL INTESTINAL TUMORS

MSCT

CT has been used for inspection of digestive tract tumors since the 1980's with spiral CT becoming available in 1989. With fast speed, large volume data acquisition and contrast-enhanced scanning, CT observation of small intestinal tumors has progressed. The development of MSCT technology in 1998 allowed data acquisition over the entire abdomen in thin slices within one breath-hold, leading to fewer peristaltic and breathing artifacts. In addition, MSCT also has many other advantages, such as high spatial resolution and powerful post-processing of the images. It is widely accepted that MSCT can be used for the investigation of intestinal pathologies. Computed tomography enteroclysis (CTE) is used to perform enhanced MSCT scanning and image post-processing after the small intestine is distended by administering a high volume of contrast medium orally or *via* a nasojejunal catheter.

Oral ingestion of contrast medium is easy to perform and is tolerated by most patients. However, a high volume of contrast medium (1500-2000 mL) is required to make the small intestine sufficiently distended. Administration *via* a nasojejunal catheter is efficient for small intestinal distension, but this procedure produces additional discomfort to patients. In addition, the speed of pumping the contrast medium *via* the nasojejunal catheter needs to be strictly controlled. Contrast agents used for small intestine distension can be divided into low-density contrast medium (e.g. water, methyl cellulose solution and air) and high-density contrast medium (e.g. 2% meglucamine diatrizoate solution)^[4-6]. Previous studies^[7] showed that low-density contrast agent can efficiently display small intestine wall enhancement that is located between the hypodensity of the intraluminal fluid and the hypodensity of the extraluminal fat tissues. Furthermore, a low-density contrast agent does not show interference with 3D angiography-like reconstructions. Our experience has shown that continuous and steady administration of 2.5% mannitol solution (2000 mL) orally within 30 min can ensure adequate distension of the entire small intestine. Mannitol solution (2.5%) is one type of isotonic solution that is not easily absorbed by the small intestine. Application of anticholinergic drugs before scanning can boost the distension of the small intestine. 16-MSCT and 64-MSCT can acquire data in the arterial and venous phases of contrast-enhanced scanning in thin slices after plain scanning. These data are used for multiplanar reconstruction to obtain isotropic images in sectional, coronal and sagittal directions, which is helpful to depict intestinal wall and small lesions. At the same time, maximum intensity projection and volume rendering technique reconstruction can be performed to identify blood vessel occlusion and stenosis^[8-12].

CTE, which is easy to perform and produces less complications, can display the cavity and wall of small

intestine, parenteral lymph nodes, mesentery, mesenteric vessels and the adjacent structures. It can be applied to observe a variety of intestinal pathological changes. In addition, CTE can accurately display the mucosal lesions, thickening of the wall and parenteral complications. CTE can also differentiate between outward growth and inward growth tumors, indicate whether the tumor is lobulated or whether there is internal necrosis, depict the depth of infiltration, and determine the types of pathological changes based on the general morphology of the tumors. Furthermore, it can also be used to identify metastasis over time using the entire abdominal scan, to make accurate preoperative staging, to design an appropriate treatment plan and to make a prognostic evaluation^[8-14]. Conventional CT scans can show large intestinal tumors, however, they cannot provide accurate information about tumor infiltration in the intestinal wall. CTE can accurately determine the number of small intestinal tumors and can be used to make early diagnosis of small intestinal tumors. Thus, CTE is the primary choice for the detection and localization of small intestinal tumors^[13]. Boudiaf's study^[14] showed that CTE has a high sensitivity (100%) and specificity (95%) in the diagnosis of small intestinal tumors. CTE can even detect tumors that are only 5 mm in diameter.

MRI

MRI has the power to produce excellent soft tissue contrast and multiplanar imaging without radiation exposure. With the introduction of fast imaging techniques and improvement of contrast agents, magnetic resonance enteroclysis (MRE) has been widely applied for the visualization of small intestinal diseases.

Adequate cleansing of the bowel and optimal bowel distension are also required for the performance of MRI. Therefore, it is important to select a contrast agent that is not harmful to humans and has the capability of maximal bowel distension and good contrast with the intestine wall. Furthermore, the contrast agents should not introduce artifacts that may interfere with diagnosis. Based on the bowel cavity signal of T1WI, MRI contrast agents can be divided into negative contrast agents (e.g. air, diluted barium sulfate solution and methyl cellulose) that can reduce the intestine cavity signal and positive contrast agents (e.g. diluted solution of superparamagnetic iron oxide, gadolinium agent with the mixture of methyl cellulose solution) that can increase the signal in the intestine cavity. Previous studies showed that application of 2.5% isotonic mannitol solution in the MRE can achieve optimal distension and efficient contrast within the intestine wall^[15]. In T1WI sequences, mannitol solution shows low signal while the intestinal wall shows high signal after enhancement, which clearly depicts the structure of the wall. In T2WI sequences, mannitol solution shows high signal occupying the entire intestine and cavity filling defects with low signals can be fully displayed at this time. Similar

to CTE, contrast agents for MRI can be administered orally or by using a nasojejunal catheter. Before scanning, an anticholinergic drug is applied to inhibit peristalsis and reduce artifacts caused by bowel movement.

Coronal and transversal fast spoiled gradient echo (FSPGR) sequence and SE sequence (breath hold) plain scans can be performed after the application of a gas contrast agent. In addition, the scan can be repeated after Gadolinium is administered. The disadvantage of the gas contrast agent is there are obvious magnetic susceptibility artifacts on FSPGR sequences. However, there are few artifacts caused by the gas on SE sequences, except for breathing artifacts. Liquid contrast agents do not have magnetic susceptibility artifacts and performance of SE sequences is not required. The modality consists of T2-weighted coronal single-shot fast spin echo (SSFSE) sequence and T1-weighted coronal FSPGR sequence (breath hold) in the plain scan. Furthermore, an enhancement scan with a coronal and transversal FSPGR sequence (breath hold) can be performed after Gadolinium administration. Fat saturation technology can be included with SE, SSFSE and FSPGR sequences, which are described above. With its maximal luminal distension and high spatial resolution, conventional small intestinal double contrast can depict small mucosal pathological changes, but it is difficult to observe intramural or extramural lesions and parenteral complications. Moreover, it brings additional radiation exposures. MRE is a radiation-free technology, which has good soft-tissue contrast and three-dimensional imaging capability. It can not only be used to observe the mucous membrane but also reveals the pathological changes around the intestine. MRE can easily display small intestinal structures, especially in tumors with intestinal obstruction based on the signal difference generated by intestinal wall and luminal contrast agents. Studies have showed that MRE is superior to capsule endoscopy in the diagnosis of small intestinal tumors^[16].

MSCT AND MRI PERFORMANCE OF SMALL INTESTINAL TUMORS

Both primary and secondary tumors exist in the small intestine. However, the incidence of primary tumors is low, accounting for approximately 1%-3% of all gastrointestinal tumors^[2]. Secondary intestinal tumors, which originate from other parts of the body and translocate to the small intestine, are common clinically and may cause symptoms similar to primary intestinal neoplasms. When a small intestinal tumor is suspected, multiple diagnostic technologies including enteroclysis, endoscopy, MSCT, MRI or other inspections can be performed. Among those technologies, MSCT and MRI can clearly display the structure of the tumor and determine the relationship between the tumor and surrounding tissues. In addition, MSCT and MRI can reveal if there are metastases in the mesenteric lymph nodes and liver, which is important for tumor grading and treatment selection.



Figure 1 Adenoma of the ileum in a 54-year-old man who presented with a 1-year history of abdominal fullness and pain with hematochezia. Contrast-enhanced computed tomography (CT) scan shows a homogenous, moderate enhanced mass and ileocolic intussusceptions with thickening of the terminal ileum (white arrow).

Adenoma

Adenoma, the most common benign tumor, is usually asymptomatic and diagnosed incidentally. Adenoma is predominantly observed in the duodenum, especially in the periampullary regions. Adenoma is usually single, small (1-3 cm), smooth or a lobulated polypoid lesion. Multiple lesions can be observed in familial adenomatous polyposis. The typical radiologic abnormalities are the sharply defined polyp-like masses and homogenous tissue density/signal and uniform contrast enhancement on CT/MR examination (Figure 1). In some cases, it is difficult to differentiate between adenoma and intestinal polyps.

Stromal tumor

Small intestinal stromal tumor accounts for approximately 20%-30% of all gastrointestinal stromal tumors. Small intestinal stromal tumor occurs primarily in elderly patients and is usually located in the jejunum, followed by the duodenum and ileum^[17]. It is thought that stromal tumor originates from the intestinal cell of Cajal, and can be large or small in size, single or multiple in number, intraluminal, mural, or extraserosal in location. Stromal tumors are typically shown as well-circumscribed masses. Hemorrhage, cystic degeneration and necrosis may occur in the center of the tumor. CT imaging shows a round soft tissue density mass with an adjacent thickened wall. Following intravenous administration of contrast media, it is typically seen as an enhanced mass with areas of low attenuation from hemorrhage, necrosis, or cyst formation. Similar to CT scanning, MRI can depict tumors and obtain information about surrounding structures. The signal of a tumor is heterogeneous on MRI, mainly due to internal hemorrhage and necrosis. On T1-weighted images, it has low or intermediate signal intensity. On T2-weighted images, it has heterogeneous high signal intensity^[18-20] (Figure 2).

Lipoma

Lipoma, which is also one of the common benign tumors

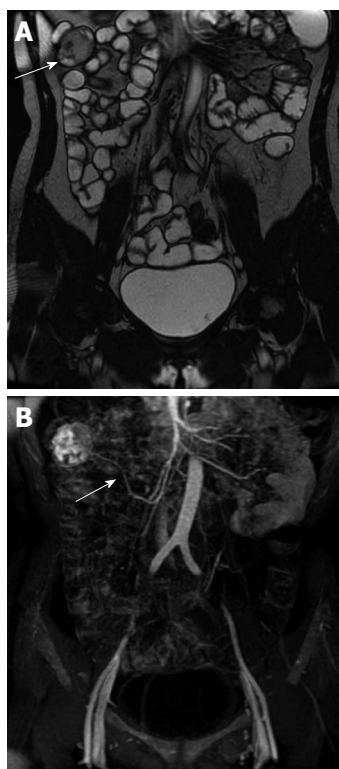


Figure 2 Gastrointestinal stromal tumor of the ileum in a 52-year-old woman who presented with persistent abdominal pain and hematochezia. A: Gadolinium-enhanced T2-weighted image shows a well-circumscribed mass with heterogeneous intermediate signal intensity (white arrow); B: MIP image shows the tumor was supplied by the superior mesenteric artery (white arrow). MIP: Maximum intensity projection.

of the small intestine, accounts for about 15% of small intestinal tumors. It originates from adipose tissue in the intestinal submucosa and usually locates in the remote small bowel. Lipoma is usually observed as a single tumor that is 1-6 cm in diameter. Lipoma can cause intussusception, which is the most frequent triggering factor of intussusception in adults. Intussusception is usually the first symptom of lipoma. The typical performance of lipoma on CT/MR images is the sharply demarcated, homogeneous fat-tissue density/signal mass closely related to the slightly thickened intestinal wall. Hounsfield units range between -80 and -120^[21] (Figure 3). Fat suppression MR sequences can provide additional assistance for a clear diagnosis.

Adenocarcinoma

Adenocarcinoma is the most common primary malignant tumor in the small intestine. It occurs in the junction areas between the duodenum and the jejunum. Mucosal damage and disruption, irregular bowel wall thickening and concentric mesocaval narrowing are typical observations. Sometimes, ring-like invasion, tumor-like nodules as well as ulcers can also be observed. On CT scanning, adenocarcinoma is typically manifested as an annular lesion in the proximal small intestine without a clear edge. In addition, moderate enhancement can be observed after intravenous administration with contrast medium. However, the intensity of the enhancement is less than that of stromal tumors.

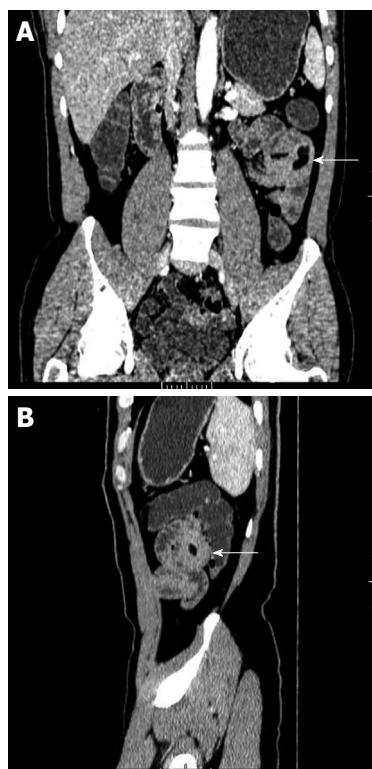


Figure 3 Lipoma of the jejunum in a 56-year-old man who presented with a 3-year history of hematochezia. A: Image (Coronal MPR) of contrast-enhanced CT scan shows a homogeneous fat-tissue density mass in jejunal smooth muscle (white arrow); B: Image (Sagittal MPR) shows obviously thickened intestinal wall (white arrow). MPR: Multiplanar reconstruction.

MRI shows asymmetric wall thickening of the small intestine, luminal narrowing, and significant heterogeneous enhancement^[19]. MRI and MSCT can observe early small tumors under the mucous membrane, can evaluate the depth of invasion of the bowel wall as well as extension outside the wall, and can display tumor metastasis in mesentery, omentum, retroperitoneal and other organs. In particular, MRI and MSCT can clearly show a tumor in the horizontal part of the duodenum and determine its relationship with the pancreas, aorta, and mesenteric vessels^[10] (Figure 4).

Carcinoid

Carcinoid is a slow-growing malignant tumor, originating from enterochromaffin cells of Kulchitsky and accounting for 1.5% of all gastrointestinal tumors. Approximately 95% of the gastrointestinal carcinoids occur in the appendix, rectum and small intestine. Besides the appendix, the small intestine is the most common site of gastrointestinal carcinoids. The small intestinal carcinoid is also the most common gastrointestinal carcinoid with clinical symptoms and often occurs in the distal ileum. Most patients with carcinoid syndrome have liver metastases, although in rare cases, the humoral load from a primary tumor may overwhelm the liver and the capacity of the lungs to metabolize serotonin. Local connective tissue proliferation stimulated by tumor secretion of 5-hydroxytryptamine is the typical appearance on CT scanning, including stellate soft tissue



Figure 4 Adenocarcinoma of the jejunum in a 38-year-old woman who presented with weight loss, abdominal pain and an abdominal mass. Contrast-enhanced CT scan shows a large, moderate enhanced soft tissue mass without a clear edge and infiltration of mesenteric vessels (white arrow).



Figure 5 Diffuse large B-cell lymphoma of the ileum in a 46-year-old man who presented with a 2-year history of abdominal pain and intermittent diarrhea and was previously suspected as having Crohn's Disease. Contrast-enhanced CT scan shows diffuse, homogeneous wall thickening of the ileum, aneurysmal dilatation of the lumen and no bowel obstruction (white arrow).

density mass^[21] calcification of some tumors. Linear strands within the mesenteric fat are probably thickened and the vascular bundles are retracted, which are indications of peritumoral desmoplastic reaction. Small tumors may be best visualized on gadolinium-enhanced T1-weighted MR images obtained with fat suppression, where they are manifested as nodules or focal areas of mural thickening with moderately intense gadolinium enhancement^[22].

Lymphoma

Primary lymphoma of the intestine occurs most commonly in the ileum, especially in the terminal ileum. Intestinal lymphomas may be polypoid, ulcerative, constrictive or aneurysmal, with the polypoid growth being the most common^[21]. Small intestinal lymphoma may appear as a circumferential bulky mass in the intestinal wall or an exophytic mass associated with thickening of intestinal walls, dilatation of the lumen and regional lymph nodes. CT and MRI imaging are useful to observe the dilated intestinal loops, regular and diffuse thickening of the intestinal walls, perforation, fistula, mesenteric edema, lymph node enlargement and other complications^[23]. Bowel-wall thickening

combined with mesenteric and/or retroperitoneal lymph node enlargement, shown as “sandwich sign,” are the main features of performance of the primary small intestine lymphoma on CT images. Aneurysmal dilatation of the lumen and mesenteric lymph node enlargement may be indications of non-Hodgkin's lymphoma (Figure 5). Diffuse thickening of the intestinal wall with multiple lesions, multiple site involvement with the same performance and multiple lymph node enlargement are suggestive of lymphoma.

Metastatic tumors

Tumor cells can spread to the small intestine through extension, hematogenous dissemination, lymphatic channels and intraperitoneal seeding. Metastatic tumors can cause symptoms similar to primary small intestinal tumors. Melanoma, carcinoma of the cervix, and lung, breast and soft tissue tumors are the common primary tumors that may spread to the small intestine. Obstruction and bleeding are common symptoms of small bowel metastases. In patients with a known history of malignancy, obstructive symptoms or bleeding from the gastrointestinal tract are indications of metastatic tumors^[21].

CT and MR play an important role in the diagnosis of metastatic tumors in the small intestine. Metastatic lesions in mesentery, peritoneal surfaces, lymph nodes and the intestinal wall can be identified by CT/MR scanning. The performance of metastatic tumors through extension results as irregular masses of intestinal wall linked to the primary tumor. Metastatic lesions in the intestinal wall can be submucosal nodules. Infiltrating lesions with diffuse thickening of the intestinal wall may be observed as well, which may result in irregular lumen narrowing. The formation of multiple metastatic nodules in the serosa, omenta and mesentery may be seen if the primary tumors contain a lot of mucus. Infiltration in mesentery and fat inside the abdominal cavity can also be seen, which may result in the increased density and thickening of the mesenteric vascular bundle. Omental fat infiltration is termed as “omental cake”. The shift and adhesion of the small intestine can be formed by pressure due to the large metastatic mass in the mesentery. Gadolinium-enhanced MR images with fat suppression can be helpful for the detection of metastases.

PROBLEMS AND PROSPECTS OF MSCT AND MRI EXAMINATION IN SMALL INTESTINE NEOPLASMS

The diagnosis of small intestine tumors, especially early detection and differential diagnosis of tumors, is still difficult although many sensitive, direct and indirect techniques have been applied. MSCT is widely used in the diagnosis of small intestine tumors, but the images obtained by MSCT are static, instantaneous and are unable to observe the details of the small intestinal mucosa. More importantly, these images cannot display the functional changes of small intestine^[13,24,25]. Meanwhile, MSCT tech-

nology with thin slices, large-scale scanning, high-resolution and multi-phase data acquisition brings increased radiation exposure, which must be given sufficient attention. Measures must be taken to optimize the scanning program to reduce radiation exposure to the patients, especially with children^[26]. Though there are still many shortcomings, such as relatively higher cost, longer time required for scanning, more mobile artifacts compared to MSCT scanning, MRI scanning is able to obtain high soft tissue contrast resolution and multi-dimensional imaging. In addition, it is non-invasive and requires no radiation exposure, which is helpful to popularize the MRI examination for small intestines^[27-32]. New technologies, such as functional cine MR imaging, have been applied to observe dynamic images of the small intestine^[31,32]. With new introductions of fast imaging techniques and shorter examination times, MRI scanning in the detection of small intestine diseases will be widely applied.

In conclusion, with the rapid development and advancement of imaging technologies, MSCT and MRI techniques will become main approaches in the diagnosis of small intestinal tumors. CTE or MRE may be the first choice for examination and diagnosis of small intestinal tumors, and in addition, combinational use of new techniques (MSCT or MRI enterography) with traditional X-ray and endoscopy (capsule endoscopy and balloon-assisted enteroscopy) will provide comprehensive information on localization, scope and features of the small intestinal neoplasms, leading to earlier diagnosis and treatment of small intestine neoplasms.

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Perspectives on the treatment of colorectal carcinoma

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Abstract

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. With 655000 deaths worldwide per year, it is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. Advances in imaging, genetics, molecular diagnostics, surgical techniques and chemotherapy are now making significant gains in our ability to prevent, diagnose, and treat this serious disease. This article reviews some of these recent successes and shares a vision of future care based on current research.

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Key words: Treatment; Colorectal carcinoma; Resection margin; Chemotherapy; Chemoprevention; Screening technology; Endoscopic submucosal surgery

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INTRODUCTION

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. With 655000 deaths worldwide per year, it is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. Advances in imaging, genetics, molecular diagnostics, surgical techniques and chemotherapy are now making significant gains in our ability to prevent, diagnose, and treat this serious disease. This article reviews some of these recent successes and shares a vision of future care based on current research.

CHEMOPREVENTION

Although colorectal cancer (CRC) is one of the most preventable forms of cancer, it remains a major cause of morbidity and mortality, and is the second leading cause of cancer death, representing a major public health concern in all developed countries. Most CRCs can be treated successfully if detected early by screening programs. Our improved understanding of colorectal carcinogenesis has facilitated the development of interventions designed to interrupt the progression of normal epithelium to cancer. Chemoprevention refers to use of synthetic or naturally occurring compounds to prevent the development of precancerous lesions (i.e. adenomatous polyps) or to reverse or delay their progression to invasive cancers. CRCs are thought to arise as a result of a series of molecular, biochemical, and histopathologic changes that transform normal colonic epithelial cells into a neoplasm, with an adenomatous polyp as an intermediate step in this process. This is a long, chronic process, therefore the window for intervention is long, possibly even decades^[1]. Molecular analyses of colorectal adenomas and carcinomas have led to a genetic model of colon carcinogenesis in which the development of cancer results not from any single genetic event but from the accumulation of a number of genetic alterations. Primary prevention strategies seek to prevent the formation of CRC in an otherwise healthy

population. Those individuals targeted may have not only predisposing genetic or environmental features, but also certain lifestyle risk factors, such as a lack of physical exercise, smoking, or alcohol intake. Secondary prevention involves patient populations who have presented with a known pre-malignant lesion or lesions, and subsequent prevention of the progression of these precancerous lesions into CRC. Finally, tertiary prevention focuses on the prophylaxis of secondary primary tumors in patients cured of their initial CRC. Chemoprevention trials have focused on these populations and include dietary or pharmacologic interventions as well as the use of nutrients in order to suppress or reverse the carcinogenic process. The best candidates for chemo-prevention include those individuals at high risk for development of CRC, such as those with a previous history of colorectal adenomas or carcinomas, those with familial adenomatous polyposis (FAP), and those with metabolic syndromes, especially with abdominal obesity and insulin resistance^[2]. New issues regarding the theoretical and clinical basis of chemo-prevention, however, have emerged, and questions regarding cardiovascular safety and other therapeutic indices have recently come up as barriers to the use of, for example, selective cyclooxygenase-2 inhibitors^[3]. Substantial evidence has shown that several drugs could have chemopreventive benefit. Chemoprevention clinical trials have shown no benefit with fiber or antioxidant interventions. Current data are insufficient to support the use of HRT to reduce the risk of CRC. Use of 5-ASA, UDCA, statins, calcium, vitamin D, folate, and selenium as chemopreventive agents seems to be promising, and further clinical trials will help to elucidate their chemopreventive potential^[4], and it is important that bacteria microflora modulates gut environment and mucosal immunity, and immune regulation (both at local and systemic level) in cancer development^[5]. Any protective benefit must be balanced against the potential side effects of the long-term ingestion of any putative chemopreventive agent. The risk (i.e. gastrointestinal complications) of regular use of ASA or conventional NSAIDs may outweigh the potential benefits in preventing CRC in populations at low risk. Chemoprevention cannot yet be accepted as standard medical practice. Chemoprevention should not replace a periodic fecal occult blood test (FOBT) and colonoscopic surveillance, as well as lifestyle modifications in view of known risk factors, such as reduction in the intake of red meat, appropriate physical exercise, smoking cessation, or weight control. Future studies will have to clarify the role of chemopreventive agents in CRC^[6].

NEW CRC SCREENING TECHNOLOGIES

There are now multiple CRC screening tests that vary in their ability to detect the different stages in the adenoma to carcinoma sequence. The original guaiac-based CRC test (Hemoccult II) was used to detect CRC at an early stage. Most of the newer tests have at least some capacity to

detect the larger adenomas and thus reduce CRC incidence as well as mortality. The different types of CRC screening tests are used according to the requirements of different stages of intervention, degree of invasiveness, frequency of repeat testing, and level of acceptance by patients. FOBT is the only CRC screening approach demonstrated to be effective in randomized controlled trials^[7]. Depending on whether the tests were done biennially or annually, and whether they were rehydrated or not, FOBT was associated with a 15%-33% reduction in CRC mortality, and a 17%-20% reduction in CRC incidence. The guaiac tests use the peroxidase activity of heme or hemoglobin as an indicator of occult blood. The FIT is based on detection of human globin. These tests were developed as a quantitative test for occult blood in the stool that did not require the 3 d dietary restrictions of the Hemoccult II test. FOBT, although not as sensitive for colorectal adenomas as colonoscopy, CT colonography or flexible sigmoidoscopy, offers the advantage of being noninvasive, and convenient for individuals. Colonoscopy was first introduced in the 1970s as a method to visualize the entire colon^[8]. In 1973, Wolff *et al*^[9] demonstrated the feasibility of colonoscopic polypectomy that initiated the use of colonoscopy as both a diagnostic and therapeutic tool. Fiberoptic colonoscopes were replaced by digital video-endoscopy that enhanced visual detection of polyps and provided a record of the reach to the cecum, postpolypectomy site, and cleanliness of the bowel. Technical improvements have facilitated polyp removal and maneuverability within the colon and rectum. Colonoscopy can be used as the primary screening tool or as the diagnostic and therapeutic tool after a positive FOBT, flexible sigmoidoscopy, or CTC test. The key conceptual basis for CTC-also called "Virtual Colonoscopy" or VC-arose over a decade ago, when it was recognized that thin-slice contiguous abdominal CT images could be reconstructed in software to simulate visualization of the lumen of the colon and create a "fly-through" display presenting polyps as prominent irregularities. It took a dozen years for this approach, combined with other improvements, to reach maturity. Between 2000 and 2002, commercial multirow detector CT scanners advanced from 4-row detector devices to 64-row assemblies, enabling high-speed imaging of the total abdomen within a single breath-hold, thus nearly eliminating motion artifacts that had bedevilled earlier efforts. Hardware and software innovations also made multiplanar displays visually-compelling 3D dynamic simulations possible. Magnetic resonance (MR) imaging is an accurate method of predicting the possibility of achieving a surgically clear circumferential resection margin (CRM), preventing incomplete surgical resection of the tumor, which will eventually increase the risk of local recurrence and allow a better chosen selection of patients for neo-adjuvant treatment. In addition, the diffusion-weighted MR imaging yields better diagnostic accuracy than the use of conventional MR imaging alone in the evaluation of patients with locally advanced rectal cancer^[10].

Fecal DNA testing represents a new noninvasive approach to CRC screening. The approach has been made

possible by elucidation, over the last 2 decades, of the molecular “pathway” or changes that occur as colon mucosa progresses from normal tissue to adenoma and to CRC. These changes provide “targets” that an assay can be designed to detect. Simultaneous technological advances have allowed human DNA to be separated and purified from stool and to be amplified and analyzed. An approach that measures DNA in stool has at least a theoretical advantage over an approach that measures bleeding, like FOBT. The possible theoretical advantage of stool DNA testing is that, because cancer is a disease of multiple mutations, a stool DNA assay might be made “sensitive enough” if the right markers can be discovered and measured. The first-generation DNA assay that was tested included multiple mutations of the *APC*, *K-ras*, and *P53* genes that are in the “pathway” described by Vogelstein *et al*^[11] along with BAT-26, a marker of mismatch-repair pathway tumors^[12]. In the future, the potential usefulness of stool DNA testing may be affected by different factors such as sensitivity, specificity, and commercial cost.

CHEMOTHERAPY

Despite many recent therapeutic advances CRC remains a major problem throughout the world, affecting close to 1000 000 people worldwide, with half of them dying within 10 years of surgery. Significant management advances in the adjuvant and advanced settings have been presented, thus improving our understanding of the biology of the disease, and allowing better individualization of patient treatment.

Among the most interesting advances are the findings of a study showing that K-RAS mutations were associated with shorter progression-free survival (PFS), and that patients with colon cancer expressing a wild-type form of the KRAS gene respond better to epidermal growth factor receptor (EGFR) inhibitors than those in whom KRAS is mutated^[13]. Most notably, and with immediate effect, the European Medicines Agency has restricted the use of cetuximab as a first-line treatment for patients with colon cancer to those whose tumors have the wild-type KRAS gene.

Adjuvant treatment

Two important abstracts from the National Surgical Adjuvant Breast and Bowel Project (NSABP), focused on adjuvant chemotherapy. NSABP C-07^[14] enrolled over 2400 patients after radical surgery. They received either a weekly schedule of 5-fluorouracil (5-FU; 500 mg/m² bolus) followed by folinic acid (FA; 500 mg/m²) weekly for 6 wk repeated three times, or the same combination given with intravenous oxaliplatin, 85 mg/m², on days 1, 15 and 28 (the FLOX regimen). In the NSABP C-08 trial, 2700 patients with CRC were assigned randomly to bevacizumab or a placebo, in addition to oxaliplatin-based chemotherapy. This trial reported the safety of bevacizumab administered with chemotherapy after radical surgery. The CPT-GMA-301^[15] study evaluated postoperative irinotecan combined with 5-FU (the FOLFIRI regimen) versus 5-FU in patients

with radically resected liver metastasis and no evidence of extrahepatic spread, who had not received preoperative chemotherapy. This latest negative trial shows that irinotecan-based regimens are not effective in the adjuvant setting. After potentially curative surgery, irinotecan does not yet have a proven role.

Advanced disease

Using Oxaliplatin and cetuximab in first-line therapy treatment of metastatic colorectal cancer (OPUS)^[16], a first-line randomized phase II trial enrolled 340 patients who received either FOLFOX alone or with cetuximab. The primary endpoint response rate was higher in those patients receiving the combination treatment, although this did not reach statistical significance, and did not impact on PFS. The development of EGFR inhibitors has influenced the field of targeted therapeutics significantly. Unfortunately, the benefits of EGFR inhibitors are limited by several drug resistance mechanisms, which include KRAS mutations^[17]. Analyses of KRAS status in relation to efficacy showed that patients with KRAS wild-type tumors had significantly better outcomes with FOLFOX and cetuximab than with FOLFOX alone. In contrast, those with KRAS-mutated tumors did significantly worse when cetuximab was added to chemotherapy.

In the EVEREST trial, patients were treated with first-line irinotecan and cetuximab then randomized either to continue standard dose cetuximab or to receive dose-escalated cetuximab, in the absence of clinically significant skin toxicity, after 3 wk of treatment^[18]. Several key findings came out of this. Firstly, patients with wild-type KRAS had better outcomes in terms of response rate and PFS, than those with KRAS-mutated tumors had. Secondly, escalating the dose of cetuximab appeared to enhance efficacy only in patients with KRAS wild-type tumors. In conclusion, skin toxicity and KRAS wild-type status were independent predictors of better outcomes in patients receiving cetuximab. Dose escalation did not overcome the adverse impact of having a KRAS-mutated tumor.

Taken as a whole, these data represent a major milestone in our ability to personalize therapy and increase the cost-effectiveness of treating patients with advanced CRC using anti-EGFR antibodies. KRAS testing represents the first predictive biomarker that differentiates those patients who are likely to respond to EGFR inhibitors from those who are not.

Although the mechanism of action of VEGF antibodies is still a subject of investigation and study, the anti-VEGF antibody bevacizumab has been approved for the treatment of various solid cancers, including colorectal cancer. As bevacizumab has been integrated into the treatment of many different types of cancers, the development of bevacizumab-resistant tumors has become more common. Recent studies show that targeting other angiogenesis-signaling pathways such as platelet-derived growth factor-C, Bombina variegata peptide 8 and VEGFR-3 may lead to enhanced response in anti-VEGF resistant tumors^[19]. In the future, tailored treatments

consisting of combinations of chemotherapy, other targeted therapies and anti-angiogenesis agents will hopefully result in better patient outcomes.

Prolonged administration of oxaliplatin is associated with cumulative peripheral neurosensory impairment, and the best strategy to counteract this dose-limiting toxicity remains unclear. Two trials' abstracts addressed the question and tested the putative neuroprotective role of calcium/magnesium supplementation. Unfortunately, both trials closed prematurely and definitive conclusions are hard to draw. These data do not show any deleterious effect of calcium/magnesium supplementation in patients receiving oxaliplatin-based chemotherapy. Indeed, such supplementation may reduce neurotoxicity. Nevertheless, in the authors' opinion, with data from fewer than 300 patients, calcium/magnesium supplementation cannot be recommended.

RESECTION MARGINS IN MODERN RECTAL CANCER SURGERY

At present, the preferred treatment for rectal cancer is low anterior resection with total mesorectal excision and sphincter preservation. Complete removal of the tumor's lymphatic and vascular pad with free resection margins has led to a reduction in rates of local recurrence and improved disease-specific survival. In addition to considering the distal and proximal margins from the tumor edge, for an optimal outcome, it is essential to consider distal mesorectal spread and the circumferential mesorectal margin.

Distal resection margin

The removal of lower rectal tumors with sphincter preservation was made possible by the introduction of surgical staplers, and revision of the traditional 5-cm resection margin. Reports in the 1990s that intramural submucosal spread, noted in 40% of patients, extended for more than 1 cm distally in only 4%-6% of cases, led to the general acceptance of a 2-cm distal margin as adequate. Others showed that distal margins even smaller than 2 cm did not increase local recurrence rates or compromise 5-year survival^[20]. To preserve the sphincter in patients with ultra-low rectal cancer, Schiessel *et al.*^[21] introduced the technique of transanal resection of part or the entire internal anal sphincter, whereby bowel continuity could be restored with proper distal margins. Using intersphincteric resection in 92 patients with a tumor at 1.5-4.5 cm (mean 3 cm) from the anal verge, Rullier *et al.*^[22] achieved negative margins in 98% of cases; local recurrence was found in 2%. Factors associated with distal tumor spread beyond 1 cm consist of advanced stage at diagnosis and histologically aggressive disease, namely, poorly differentiated cancer and lymphovascular and perineural invasion. These factors also predicted poor prognosis, regardless of the length of the distal margin. A National Cancer Institute (NCI) Expert Panel Guidelines series published in 2000, recommended a distal margin length of 2 cm as ideal, with margins of 1 cm being acceptable in low rectal tumors^[23].

Distal mesorectal margin

Heald *et al.*^[24] pioneered the use of TME, and reported distal mesorectal spread of 4 cm from the distal tumor edge. Hida *et al.*^[25] noted that in patients with pT3 and pT4 rectal cancer, the extent of distal mesorectal spread was related to tumor location. The longest distance to a metastatic node was 2 cm. in carcinoma of the rectosigmoid, 4 cm. in carcinoma of the upper rectum, and 3 cm. in carcinoma of the lower rectum. They therefore concluded that a mesorectal margin of at least 5 cm. is required in the surgical treatment of locally advanced rectal cancer. They postulated that blockage of the upward lymphatic flow by the locally advanced cancer produced a downward spread in the mesorectum. They also suggested a 4-cm. mesorectal margin for adequate oncologic resection.

CRM

The CRM, also termed the radial resection margin, corresponds to the non-peritonealized surface of the resection specimen created by dissection of the subperitoneal aspect at surgery. The term CRM is specific to rectal tumors (and does not apply to large intestinal cancers in general). The posterior CRM is triangular, and runs up towards the sigmoid mesocolon; the anterior CRM is located in the most distal aspect of the specimen. The preoperative identification of patients at high risk of a positive CRM prior to surgery has improved with advances in magnetic resonance imaging (MRI) techniques. Recent data from the prospective, multicenter MRI and rectal cancer European equivalence study confirmed the accurate prediction of both T stage and CRM clearance of 1 mm. of the resection margin using MRI. The accurate determination of the CRM status is essential, because it is the single most important factor for predicting the risk of local recurrence in patients with rectal cancer. A positive CRM is defined as continuous or discontinuous tumor extension, or the presence of a positive lymph node < 1 mm. from the radial, nonperitonealized soft tissue edge. A positive CRM is associated with higher disease stage, higher histology grade, and tumor infiltration^[26]. A radial margin of less than 1 mm. was predictive of an increased risk of distant metastases (37% *vs* 15%) and shorter survival (70% *vs* 90%). Other factors directly related to a positive CRM are the surgical technique used, and the tumor location. The CRM was found to be positive in 7.3% of 1113 patients after TME or PME compared to 17% of 2450 patients after conventional blunt rectal dissection. Others reported that lower and anterior rectal tumors are at greater risk of a positive CRM, with a correspondingly dismal prognosis. This finding might be explained by the thinner mesorectum in these locations. Bernstein *et al.*^[27] studied 3194 patients with known CRM status, and made the conclusion that a CRM of 2 mm. or less had an impact on the prognosis of T2 and T3 tumors located 6-15 cm above the anal verge, but not on lower tumors. A CRM of 2 mm. or less confers a poorer prognosis, and patients should be considered for neoadjuvant treatment.

ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection allows en-bloc resection of a lesion, irrespective of the size of the lesion^[28]. Endoscopic submucosal dissection (ESD) has been established as a standard method for the endoscopic ablation of malignant tumors in the upper gastrointestinal (GI) tract in Japan^[29].

Although the use of ESD for colorectal lesions has been studied *via* clinical research, ESD is not yet established as a standard therapeutic method for colorectal lesions because colorectal carcinoma has unique pathological, organ-specific characteristics that differ radically from those of the esophagus and stomach, and scope handling and control is more difficult in the colorectum than in the upper GI tract. Depending on the efficacy of endoscopic mucosal resection (EMR) and the clinico-pathological characteristics of the colorectal tumor, the proposed indications for colorectal ESD are as follows: (1) lesions difficult to remove en bloc with a snare EMR, such as nongranular laterally spreading tumors (particularly the pseudo depressed type), lesions showing a type VI pit pattern, and large lesions of the protruded type suspected to be carcinogenic; (2) lesions with fibrosis due to biopsy or peristalsis; (3) sporadic localized lesions in chronic inflammation such as ulcerative colitis; and (4) local residual carcinoma after EMR. Saito *et al.*^[30] treated a total of 400 patients for 405 lesions with ESD. The en-bloc resection rate was 87% and the curative resection rate was 86%, and the perforation rate was 3.5%. ESD is a feasible technique for treating large superficial colorectal tumors because it provides a higher en-bloc resection rate and is less invasive than surgical resection. It also provides precise histologic information^[31]. Colorectal ESD is currently in the development stage, and a standard protocol will be available in the near future^[32].

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Peroxisome proliferator activated receptor- γ and the ubiquitin-proteasome system in colorectal cancer

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Abstract

Peroxisome proliferator activated receptor- γ (PPAR γ), a transcription factor of the nuclear receptor superfamily plays a significant role in colorectal cancer pathogenesis. In most experimental systems PPAR γ activation has tumor suppressing effects in the colon. PPAR γ is regulated at multiple levels by the ubiquitin-proteasome system (UPS). At a first level, UPS regulates PPAR γ transcription. This regulation involves both PPAR γ transcription specific factors and the general transcription machinery. At a second level UPS regulates PPAR γ and its co-factors themselves, as PPAR γ and many co-factors are proteasome substrates. At a third level of regulation, transduction pathways working in parallel but also having interrelations with PPAR γ are regulated by the UPS, creating a network of regulation in the colorectal carcinogenesis-related pathways that are under UPS control. Activation of PPAR γ transcription by direct pharmacologic activators and by stabilization of its molecule by proteasome inhibitors could be strategies to be exploited in colorectal cancer treatment.

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INTRODUCTION

Peroxisome proliferator activated receptor γ (PPAR γ) is a transcription factor of the nuclear hormone receptor superfamily. It has an important role in adipose tissue and in adipogenesis but is also expressed at high levels in colonic epithelium. PPAR γ is involved in colorectal carcinogenesis and PPAR γ -dependent transcription has anti-carcinogenic effects in many experimental colorectal cancer models while in some other instances PPAR γ displays cancer promoting effects^[1].

The ubiquitin proteasome system (UPS) is a cellular regulatory machinery that leads to the degradation of multiple proteins as a mode of permanent down-regulation. Virtually all cellular processes are regulated by the UPS including processes involved in carcinogenesis such as cell cycle, apoptosis, signal transduction and DNA transcription^[2]. Included in UPS-regulated processes are signal transduction effecting PPAR γ activation and PPAR γ -dependent transcription. PPAR γ regulation by UPS as it pertains to colorectal cancer pathogenesis will be the subject of this editorial review.

PPAR γ AND PPAR γ -DEPENDENT TRANSCRIPTION

PPAR γ together with two other PPARs (PPAR α and PPAR β/δ) belongs to the orphan ligand sub-family of the nuclear hormone receptor super-family. Human PPAR γ

gene is located at chromosome 3p25^[3]. Higher levels of protein expression are displayed in adipose tissue and colonic epithelium but many other tissues such as pancreatic β cells and vascular endothelium also express the transcription factor^[4].

PPAR γ molecule has a domain organization similar to all nuclear receptors. In the amino-terminal part of the protein there is a transcription regulation domain, followed by a DNA binding domain and a hinge region, while the carboxy-terminal part of the molecule is occupied by the ligand binding domain.

Various lipids such as prostaglandin 15d-PGJ₂, arachidonic acid and eicosapentaenoic acid have been found to represent natural PPAR γ ligands but the optimal ligand in different physiologic conditions *in vivo* is not well established^[5,6]. Synthetic ligands of PPAR γ have also been described, the most prominent of which are thiazolidinediones, a family of drugs that are used in the clinic as anti-diabetics^[7]. After ligand binding, PPAR γ undergoes a conformational modification, binds to co-activators and enters the nucleus to bind peroxisome proliferator response elements (PPREs) on target gene promoters. With the aid of co-activators such as PGC-1 α (PPAR γ Co-activator-1 α) and Hic-5 (Hydrogen peroxide induced clone 5, alternatively named ARA55- androgen receptor activator of 55 kDa), histone acetyltransferases are recruited and acetylate histones around the transcription initiation site and pave the way for RNA polymerase to join the complex^[8-11]. Among genes induced by PPAR γ are, in addition to lipid metabolism regulating genes, cell cycle inhibitors p18, p21 and p27 and phosphatase inhibitor of akt kinase, PTEN^[12-14]. Furthermore PPAR γ acts as a suppressor of cell cycle promoters such as cyclin D and phosphatase PP2A^[15,16]. The addition of these transcriptional inductions and repressions implies that PPAR γ activity would have an anti-proliferative and anti-carcinogenic effect in tissues that display significant PPAR γ expression such as colorectal epithelium. Indeed such an effect has been observed in most, although not all, colorectal cancer experimental systems as will be discussed in a later section.

UPS

Ubiquitination, that is the covalent attachment of the protein ubiquitin to a target protein, is a post-translational modification that can result in diverse outcomes. Ubiquitin is a 76 aminoacid protein that contains several lysine residues through which different types of chains can be formed^[17]. A chain of at least four ubiquitin molecules attached to each other through a covalent link between lysine 48 of one molecule and the carboxyterminal glycine of the next molecule and finally attached to a target protein identifies this protein for proteasome degradation. Other types of ubiquitin attachments such as attachment of a single ubiquitin molecule to a target protein (mono-ubiquitination) or attachment of a ubiquitin chain to other lysine residues (e.g. Lys68) result in different outcomes and play roles in DNA repair, endocytosis, histone regulation

and nuclear export. Attachment of ubiquitin to the target requires the action of three enzymes. Initially an enzyme called E1 or ubiquitin-activating enzyme binds ubiquitin and transfers it to a second enzyme called E2 or ubiquitin conjugating enzyme using energy from the degradation of ATP to ADP. Finally, a third enzyme called ubiquitin ligase or E3 transfers ubiquitin from E2 to the target protein^[18].

After attachment of at least four ubiquitin molecules, the target protein is recognized by specific sub-units of 19S regulatory particle (RP) of the proteasome. 19S RP is a multi-protein structure that caps the two sides of the core particle (CP) of the proteasome, a cylinder shaped multi-unit structure with a hollow central chamber^[19]. Inside this chamber takes place the enzymatic degradation of target proteins executed by three enzymatic activity-possessing subunits of the CP. CP consists of four seven-member rings that are stacked one on the other. The two peripheral rings are similar to each other and are called α rings and the two central rings are also similar to each other and are called β rings. Three of the seven sub-units of the β rings, β 1, β 2 and β 5 possess the enzymatic activities of the proteasome; trypsin-like activity, chymotrypsin-like activity and post-glutamyl (caspase-like) activity respectively.

PPAR γ IN COLORECTAL CARCINOGENESIS

Given the high expression level of PPAR γ in colorectal epithelium, there is a particular interest in defining the role of PPAR γ transcription in colorectal cancer. Activation of PPAR γ after exposure of colorectal cancer cell lines to the natural ligand 15-S-hydroxy-eicosatetraenoic acid (15S-HETE) and to thiazolidinedione synthetic ligands leads to growth arrest and induction of apoptosis^[20,22]. Re-induction of differentiation related genes suppressed in colorectal cancer, such as cytokeratins 18 and 19 and intestinal alkaline phosphatase, is also noticed after activation of PPAR γ in colorectal cancer cells^[20,23]. In contrast, genes that are induced in cancer such as polyamine metabolism enzyme ornithine decarboxylase and metastasis promoting protein laminin binding protein are repressed after PPAR γ activation^[23].

Mice bearing human colorectal cancer xenografts display decreased rate of tumor growth after feeding with PPAR γ ligands^[23]. Rats in which preneoplastic colon lesions, aberrant crypt foci, have been induced by exposure to the chemical azoxymethane, also display decreased lesion formation after PPAR γ activation^[24,25]. A third *in vivo* model of PPAR γ activation using Min mice, a strain of mice with activation of adenomatous polyposis coli (APC) gene due to germline mutation, has given controversial results with some studies observing increased colonic polyps formation after PPAR γ activation^[26,27] while others have observed decreased tumor formation^[28]. Another mouse strain with APC inactivation, Apc mice, also displayed decreased polyp formation after PPAR γ activation^[29]. Overall, *in vivo* models support a suppressive role of PPAR γ in colorectal carcinogenesis^[30]. Controversial

Table 1 PPAR γ regulation by the ubiquitin-proteasome system

Degradation of PPAR γ itself
Degradation of co-activators
Degradation of inhibiting kinases
Regulation of antagonistic transcription factors (β -catenin, NF- κ B)
Degradation of calcineurin inhibitor DSCR1 (RCAN1)

PPAR γ : Peroxisome proliferator activated receptor- γ .

results with strains bearing disabled APC may relate to the fact that APC regulates the β -catenin transcription program and different residual β -catenin activity may have diverse roles in carcinogenesis^[31]. This residual activity is further modulated by increased PPAR γ activity as will be discussed later.

Induction of cdk inhibitors p21, p18 and p27 by PPAR γ is involved in cell cycle arrest following PPAR γ activation^[12,32] while interaction of PPAR γ with Rb further promotes cell cycle arrest by recruiting histone deacetylase 3 and silencing transcription^[33]. Phosphatase PTEN is a target of the PPAR γ transcription program and its induction inhibits akt kinase activation, promoting apoptosis^[14].

Expression of PPAR γ has been shown in a significant percentage of tumor specimens from colorectal cancer patients^[34,35] and has been co-related with improved prognosis in these patients^[36]. Compared with adjacent normal colonic epithelium, PPAR γ in tumor tissues displays decreased expression, further supporting a role of PPAR γ suppression in colorectal carcinogenesis^[37]. In contrast, another study reported that PPAR γ mRNA levels were increased in colorectal tumors compared with adjacent normal colon^[38]. This discrepancy may imply that PPAR γ down-regulation in colon cancer is effected at the post-translational level.

PPAR γ REGULATION BY THE UPS

Post-translational regulation of PPAR γ involves its degradation by the UPS (Table 1)^[39]. This is an event that follows ligand binding and nuclear receptor transcription activation and represents a negative feed-back regulation, a common theme in most nuclear receptors. This mechanism has been shown to regulate PPAR γ heterodimeric partner RXR as well as retinoic acid receptor, estrogen receptor, progesterone receptor and androgen receptor^[40-42]. Interestingly the two other PPAR family members PPAR α and PPAR β/δ , although structurally similar to PPAR γ , undergo a reverse regulation upon ligand binding and display delayed ubiquitination and proteasome degradation^[43,44]. PPAR γ degradation is dependent on ligand binding but independent of transcription *per se*.

PPAR γ co-activator PGC-1 α is also regulated by the UPS^[45]. PGC-1 α ubiquitination through a domain at the C-terminal part of the molecule leads to proteasome degradation. This helps in maintaining an optimal level of the co-activator for facilitation of transcription of PPAR γ and also of other transcription factors for which PGC-

1 α functions as a co-activator such as PPAR α , PPAR β/δ and estrogen related receptor α (ERR α)^[46]. Proteasome inhibition leads to ubiquitinated PGC-1 α accumulation and formation of non-functional aggregates. Thus, the UPS function maintains the optimal levels of PGC-1 α in order to perform its co-activator function^[45]. PGC-1 α is additionally regulated at the transcriptional level by both PPAR γ and ERR α , creating a regulation loop^[47,48].

PPAR γ transcriptional activity is regulated through phosphorylation by MAP kinases ERK and JNK^[49-51]. Phosphorylation suppresses PPAR γ activity in most cases but there are instances, such as the insulin-induced mitogen activated protein kinase (MAPK) phosphorylation of PPAR γ , where this phosphorylation induces PPAR γ transcriptional activity^[52,53]. Given that MAP kinases and other proteins upstream in their activation cascade, such as EGFR and akt kinase, are proteasome substrates^[54-56], this represents an additional point of regulation of PPAR γ transcriptional activity by UPS.

PPAR γ INTERACTION WITH OTHER SIGNALLING PATHWAYS AND REGULATION BY THE UPS

PPAR γ transcription factor interacts with several other factors and pathways in colorectal cancer and the final output is defined by a network of interactions in which the ubiquitin-proteasome system participates at multiple levels. Some of these interactions are outlined in the following paragraphs.

β -catenin

Abundance of β -catenin, a transcription factor activated in most human colorectal cancers, is regulated by at least three parallel pathways that culminate in its ubiquitination and proteasome degradation. The first pathway involves phosphorylation by glycogen synthase kinase 3 β (GSK3 β), facilitated by a complex in which APC takes part and results in ubiquitination by ubiquitin ligase TrCP^[57,58]. In the second pathway, ubiquitination of β -catenin is performed by ubiquitin ligase Siah-1 which is induced by p53 activation^[59,60]. In a third pathway, a currently unknown ubiquitin ligase mediates PPAR γ -activated ubiquitination of β -catenin^[61]. Tumorigenic β -catenin displays enhanced transcription activity due to mutation of serine to alanine at position 37 (S37A) rendering it resistant to GSK3 β /APC-mediated phosphorylation and ubiquitination/ proteasome degradation. This molecule can interact with PPAR γ and be ubiquitinated through an alternative mechanism in order to be degraded by the proteasome^[62]. In this way, PPAR γ suppresses β -catenin activity through enhanced proteasome-mediated degradation which possibly is a result of induction of molecules involved in the ubiquitination process^[62]. Conversely when stabilized, β -catenin inhibits PPAR γ activity, an effect requiring direct interaction of the two molecules. This interaction involves the TCF binding domain of β -catenin and a catenin binding domain in

PPAR γ that is close to the ligand binding domain of the molecule^[62]. Another study, although confirming the interaction of β -catenin with PPAR γ in colorectal cancer cells, found transactivation and not repression of PPAR γ activity in putative PPRES^[63]. Nevertheless this study used a highly artificial system in which both genes were transfected in colon cancer cell lines before co-immunoprecipitation and reporter gene experiments^[63]. Their physiologic relevance is debatable in view of the already mentioned evidence for a reverse interaction. Furthermore, in adipocytes there is a mutual antagonistic relationship between the wnt/ β -catenin signalling pathway and PPAR γ ^[64-66], strongly supporting an analogous relationship in colorectal tissue. A role of the UPS in this interaction is implied by the fact that both transcription factors are regulated by the system, although the exact regulation mechanism of the interaction must be complex.

NF- κ B

Another pathway interacting with both PPAR γ and with β -catenin signalling and that is regulated by the UPS is the one culminating in the activation of transcription factors of the NF- κ B family. NF- κ B is activated in colorectal cancer as it is down-stream of activated *K-ras*. NF- κ B has proliferative and anti-apoptotic effects and is activated in many cancers. Its main regulation is effectuated by phosphorylation and ubiquitination of its inhibitor I- κ B. This is then degraded in the proteasome, releasing NF- κ B in order to enter the nucleus and begin its transcription program. Additional regulation of NF- κ B results from direct interactions with PPAR γ and β -catenin which both result in inhibition of NF- κ B transcription^[67-69]. PPAR γ also trans-represses NF- κ B-regulated genes indirectly through binding to promoters and recruiting co-repressors. For this action, SUMOylation [i.e. Small ubiquitin-related modifier (SUMO) binding] of PPAR γ is required^[70]. Metastasis mediating chemokine receptor CXCR4 is regulated at the transcription level by NF- κ B and PPAR γ in a reciprocal way. Thus, the interaction has the potential to regulate metastasis of colorectal cancer cells, NF- κ B being a promoter while PPAR γ being a suppressor of colorectal cancer metastatic process^[71].

Given that all three transcription factors play significant roles in colorectal cancer and all three are regulated by the UPS, it is evident that a complex interaction with UPS is central in determining the final proliferation outcome of the neoplastic cell. NF- κ B is also of paramount importance in inflammation and inflammation-induced carcinogenesis. Nuclear receptors in general and PPAR γ in particular can antagonize this action, having anti-inflammatory effects^[72].

Calcium signaling

PPAR γ activation has also been found to inhibit proliferation and migration of colorectal cancer cell lines by interference with calcium signalling^[73]. PPAR γ induces calcineurin inhibitor DSCR1 (Down syndrome candidate region 1, also known as RCAN1- regulator of calcineurin 1 and calcipressin). This induction of the endogenous inhibitor

of phosphatase calcineurin results in the maintenance of transcription factor NFAT (Nuclear factor of activated T cells) in a phosphorylated and inactive form^[74]. DSCR1 was initially recognized as a protein playing a role in the pathogenesis of Down syndrome^[75] and is now recognized as playing a role in other pathologies such as Alzheimer's disease, stroke and cardiac hypertrophy^[74]. More recently its role in carcinogenesis has been described^[76]. DSCR1 is a proteasome substrate and its proteasome degradation is enhanced through the action of protein CREB (c-AMP response element-binding protein)^[77]. PPAR γ may decrease this enhanced degradation by interfering with CREB. RNA-mediated knockdown of DSCR1 results in inability of PPAR γ to inhibit colorectal cancer cell proliferation and invasion^[73], indicating the importance of this protein and of inhibiting calcium signalling in mediating PPAR γ anti-neoplastic effects. PPAR γ involvement in calcium signalling regulation is of particular relevance in colorectal cancer given the extensive cross-talk of calcium with the *K-ras* oncogene^[78].

Transforming growth factor β

Transforming growth factor β (TGF- β) is a ligand that initiates signal transduction after ligation of its cell surface receptors T β R I and T β R II. This ligation leads to activation of intracellular mediators Smad2 and Smad3 which heterodimerize with partner protein Smad4 [also called deleted in pancreatic cancer 4 (DPC4)] and enter the nucleus to activate transcription in collaboration with various other transcription factors^[79,80]. TGF- β signalling is regulated by the UPS, as Smads are proteasome substrates for degradation after ubiquitination^[81-83]. TGF- β signalling can have pro-carcinogenic or anti-carcinogenic effect depending on which other pathways are activated in a particular cell environment^[84]. In particular, MAPK activation downstream of activated *K-ras* oncogene can direct TGF- β signalling towards cancer-promotion. This is of great importance in colorectal cancers as they bear an activating *K-ras* mutation in up to half the cases. PPAR γ suppresses TGF- β 1 production through a mechanism involving inhibition of kinase p70 Ribosomal S6 kinase-1. This inhibition keeps transcription factor Zinc finger 9 in an inactive form that prevents it from transcribing TGF- β 1 gene^[85]. As a result TGF- β 1-dependent induction of chemokines Interleukin-8 and monocyte chemoattractant protein 1 is prevented^[86]. An additional point where PPAR γ and TGF- β signal transduction inter-connect is their common induction of transcription factor TSC-22 (Transforming growth factor-stimulated clone 22). This is a zinc finger transcription factor that causes growth inhibition in colonocytes through induction of CDK inhibitor p21^[87].

CONCLUSION

Colorectal carcinogenesis involves the acquisition of genetic lesions over time, leading to progression from hyperplasia to adenoma to carcinoma. Most common genetic lesions include APC mutations, activating β -catenin transcription, *K-ras* mutations and Smad4 (DPC4) mutations. All these

pathways and others involved in colorectal carcinogenesis are regulated by the UPS.

PPAR γ is a nuclear receptor transcription factor with important roles in colorectal carcinogenesis. As is the case with several transcription factors of the nuclear receptor super-family, it is regulated by the ubiquitin-proteasome system. This system modulates PPAR γ action not only by directly degrading the transcription factor itself but also through other transcription factors and other proteins working in parallel as a network. These multiple levels of regulation will have to be taken into account, using the new tools of molecular biology such as whole genome interrogations, when designing new rational targeted therapies and combinations. Both PPAR γ and the UPS have been manipulated pharmacologically in the clinic, the former with the use (for the treatment of diabetes) of activators thiazolidinediones and the latter with the use of the proteasome inhibitor bortezomib. A combined use in order to activate the transcription factor in at least two levels could be attractive for the development, of drugs for the treatment of colorectal cancer. Determination of subsets of colorectal cancers that, due to specific molecular lesions, could be particularly sensitive to PPAR γ activation would be of importance in this development.

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Intermittent gastric outlet obstruction caused by a prolapsing antral gastric polyp

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Abstract

Most gastric polyps have an asymptomatic presentation and are an incidental finding on upper endoscopy. Symptomatic presentations can range from an ulcerated polyp leading to anemia and occult bleed to complete gastric outlet obstruction. We report a case of an 89-year-old woman who presented with postprandial nausea and early satiety. Her upper endoscopy revealed a 2 cm pedunculated hyperplastic polyp arising from the antrum of the stomach which was seen prolapsing into the pylorus causing intermittent gastric outlet obstruction. In the present report, we statistically analyzed 39 prolapsing gastric polyps previously reported in the English literature and demonstrate the current utility of monopolar snare polypectomy in establishing a histological diagnosis while offering simultaneous treatment. Additionally, we review the literature for the management of all hyperplastic gastric polyps in relation to advancements in digestive endoscopy.

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Key words: Hyperplastic polyps; Stomach; Endoscopy

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INTRODUCTION

Gastric polyps are usually an incidental finding on upper endoscopy with an incidence of 1%-5%^[1-2]. Rarely, larger gastric polyps can present with symptoms. Symptomatic presentations can range from an ulcerated polyp leading to anemia and occult bleeding to complete gastric outlet obstruction. We describe a case of intermittent gastric outlet obstruction by a hyperplastic antral polyp and its subsequent management. We also review the literature for the management of hyperplastic gastric polyps in relation to advancements in digestive endoscopy.

CASE REPORT

An 89-year-old woman with hypertension presented for evaluation of intermittent postprandial nausea and dull epigastric pain for 3 mo. She complained of early satiety and a 2.3 kg weight loss. She denied dysphagia or any change in bowel habits. On exam, her abdomen had normoactive bowel sounds and mild tenderness over the epigastrium. She had a negative Murphy's sign. The liver and spleen were not palpable. At admission, laboratory tests revealed hemoglobin of 11.2 g/dL with a mean corpuscular volume of 78.5 fL. Serum iron was 57 µg/dL and total iron-binding capacity was 346 µg/dL. Upper and lower gastrointestinal endoscopies were recommended because of the patient's epigastric pain and iron deficiency anemia. Upper endoscopy exposed a 2 cm pedunculated polyp arising from the antrum of the stomach. This polyp was

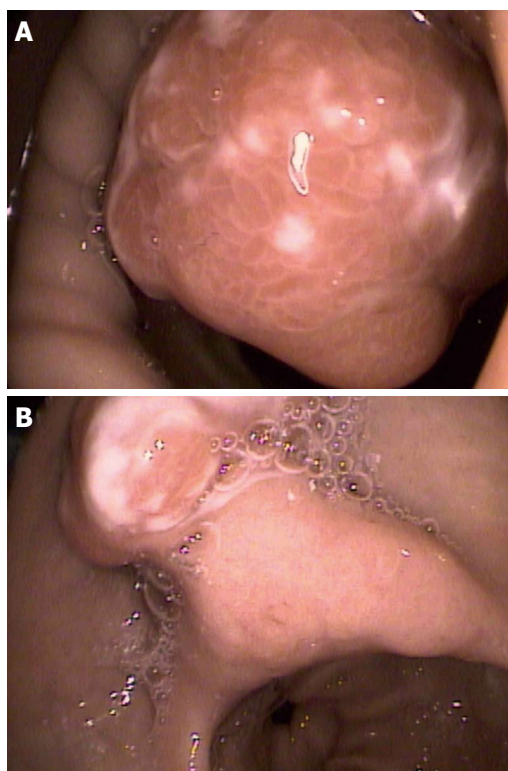


Figure 1 Polyp was seen prolapsing into the pylorus of the stomach causing intermittent gastric outlet obstruction.

seen prolapsing into the pylorus of the stomach causing intermittent gastric outlet obstruction (Figure 1A and B). The polyp was excised with monopolar snare polypectomy and sent for pathology. Pathology revealed a hyperplastic polyp without metaplasia, dysplasia, or malignancy (Figure 2). Furthermore, the surrounding antrum was biopsied for pathology, which showed chronic inactive gastritis and negative staining for *Helicobacter pylori* (*H. pylori*). Colonoscopy was unremarkable. After excision of the polyp, the patient returned to the GI Clinic 2 wk post procedure with complete resolution of her Abdominal pain symptoms.

DISCUSSION

This patient had a hyperplastic antral gastric polyp causing intermittent gastric outlet obstruction. These cases are sporadically reported in the literature. Short *et al*^[3] reviewed 30 prolapsing gastric tumors reported in the English literature up to 1965. In the present report, we analyzed the past 39 gastric polyps leading to gastric outlet obstruction found in the English- literature^[4-36] (Table 1). Furthermore, we reviewed the literature for the management of both symptomatic and asymptomatic hyperplastic gastric polyps. Prior to the advent of endoscopy, physicians relied on characteristic intraluminal filling defects on radiography and subsequent laparotomy for definitive treatment of symptomatic gastric polyps^[4]. Nonoperative endoscopy has reduced the surgical risk of open laparotomy. One of the first reported cases treated by endoscopy was by Brandt *et al*^[5] in 1973. He removed a 1.5 cm pedunculated

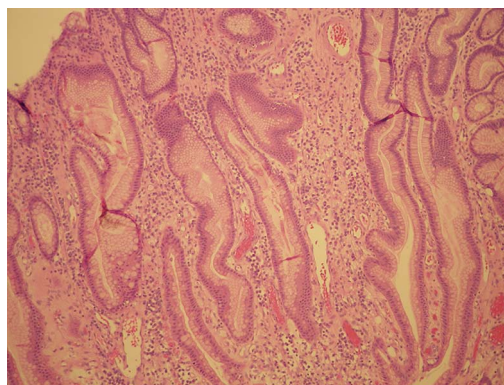


Figure 2 Pathology revealed a hyperplastic polyp without metaplasia, dysplasia, or malignancy.

adenomatous polyp with snare polypectomy in a sixty-five year old female who presented with postprandial midepigastric pain.

Gastric polyps causing gastric outlet obstruction seem to be more prevalent in elderly females with a 64 percent female predominance (23 patients) and a median age of onset of 72 years in female^[4-11,17,19,22,23,25,27-29,32-35] adults. Race was not specified in the majority of cases. Only four pediatric cases have been reported^[13,14,16,18]. The pediatric cases presented within the first year of life, mimicked pyloric stenosis, and required surgical removal. In adults, case presentations ranged from mild epigastric pain to more dramatic presentations of severe iron deficiency anemia^[26] and even acute pancreatitis^[22,29]. The majority of symptomatic gastric polyps had an antral location with a median size of 5 cm (range 1.5-13 cm)^[4,6,8,10-12,15,17,19-22,25-27,29,30,33,35]. The median size of polyps removed endoscopically was 3 cm (range 1.5-8 cm)^[6,11,17,21,25-27,29,30,33,35], while the median size of surgically removed polyps was 6 cm (range 3.5-13 cm)^[4,8,10,12,15,17,19,20,22,36]. Kumar *et al*^[17] have reported the largest endoscopically treated polyp causing intermittent gastric outlet obstruction to date. They removed an 8 cm polyp: two-thirds of the polyp was snared and the remainder excised at a subsequent visit. Histologically, there were 15 hyperplastic polyps^[7,11,17,19,21-23,25-27,30,34,35], 5 adenomas^[5,8,10,17,31], 4 adenocarcinomas^[8,12], 3 lipomas^[15,20,24], 2 inflammatory^[32,33], and 1 leiomyoma^[17]. The other cases only specified the polyp as benign^[4,6,9,28,29]. Of the polyps reviewed, 7 harbored malignancy^[7-8,12,31].

The particular importance of gastric polyps is their tendency towards malignancy. In our patient, we were not only able to establish a histopathological diagnosis at the time of upper endoscopy but also offer definitive therapy. However, there are no set guidelines for the optimal management of all gastric polyps at the time of initial upper endoscopy. For a symptomatic polyp, endoscopic or surgical excision is often pursued to relieve symptoms and to achieve a histological diagnosis. The management strategy is less clear in asymptomatic gastric polyps. Certainly, the rate of malignant transformation varies among the different histological subtypes of gastric polyps. Fundic gland and inflammatory fibroid polyps have virtually no malignant potential. Hyperplastic polyps have

Table 1 Characteristics of gastric polyps leading to gastric outlet obstruction

Characteristics	
Adults (n)	36
Sex (n)	
Male	13
Female	23
Age (yr)	
Median	70
Range	41-89
Size of all polyps (cm)	
Median	5
Range	1.5-13
Size of endoscopy removed (cm)	
Median	3
Range	1.5-8
Size of surgically removed (cm)	
Median	6
Range	3.5-13
Histological subtype (n)	
Hyperplastic	15
Adenoma	5
Adenocarcinoma	4
Lipoma	3
Inflammatory	2
Leiomyoma	1
Benign unspecified	6

up to a 2.1% rate of malignant transformation^[37,38], and the rate is significantly higher for adenomatous polyps (up to 40%)^[39].

Unfortunately, besides fundic gland polyps which have a clear typical feature, upper endoscopy cannot reliably distinguish the type of gastric polyp by gross inspection. Therefore, it is important to make a histopathological diagnosis, although whether to biopsy or excise gastric polyps is not always clear. Forceps biopsy can come with sampling error^[40,41], and polypectomy has its own risks, such as bleeding and perforation with rates of 7.2% and 0.45%, respectively^[40].

Because of the risks associated with polypectomy, some authors have recommended conservative medical management and endoscopic surveillance of smaller hyperplastic polyps. Although the exact pathogenesis is not known, hyperplastic polyps have been associated with chronic inflammation and irritation of the gastric mucosa. *H. pylori* infection is the most commonly associated condition that predisposes hyperplastic gastric polyp formation. *H. pylori* associated hyperplastic polyps show increased cyclooxygenase-2 (COX-2) expression. The importance is that COX-2 expression plays an important role in tumor enlargement, partly through enhanced angiogenesis^[42]. Several prospective studies have demonstrated the regression of hyperplastic polyps after eradication of *H. pylori* infection^[43-45]. However, not all hyperplastic polyps are associated with documented *H. pylori* infection, and there are no data demonstrating regression of hyperplastic polyps greater than 1 cm in diameter after *H. pylori* treatment. Less common associations include autoimmune gastritis, environmental gastritis, chemical gastropathy, Zollinger-

Ellison syndrome, cytomegalovirus gastritis, amyloidopathy, gastric antral vascular ectasia, post-antrectomy stomach^[46], and post solid organ transplant recipients^[47,48].

A hyperplastic process in response to these tissue insults gives hyperplastic polyps their characteristic histological features. Hyperplastic polyps consist of dilated, elongated, architecturally distorted foveolar epithelium with a surrounding edematous stroma holding varying degrees of active and chronic inflammation. Rarely, dysplasia and carcinoma may occur within and around the polyp. If adenocarcinoma is found after polypectomy, a synchronous adenocarcinoma in another part of the stomach maybe found in up to 30% of cases^[49]. Therefore, it is prudent to investigate surrounding polyps and to biopsy the surrounding gastric mucosa for associated gastritis and pathology.

The possible relationship between gastric hyperplastic polyps and gastric cancer remains unknown. Different molecular biologic factors in hyperplastic gastric polyps have been investigated for gastric carcinogenesis. Jain *et al*^[50] reviewed the literature for these mechanisms and found over expression of *p53* gene mutation, Ki-67 labeling indices, and microsatellite instability as the most implicated markers. Other markers such as ERB-2, APC, DCC, LOH at 17p have not been found in association with dysplasia. Future studies which are designed to identify the utility of analytical tests such as gene array and microsatellite instability testing to predict which hyperplastic polyps carry malignant potential are needed. Currently, the only prognostic factor is polyp size. Ginsberg *et al*^[51] demonstrated that cancer risk increases with polyp size and recommended all polyps greater than 0.5 cm be removed regardless of the histological subtype.

The clinical significance of larger gastric polyps is this risk of malignancy. As a result most gastroenterologists advocate the excision of polyps greater than 0.5 cm with biopsies of the surrounding gastric mucosa. Most labs use electrocautery snare polypectomy, but some polyps, specifically sessile polyps, may not be amenable to this technology because of the risk of bleeding and perforation. Endoscopic mucosal resection (EMR) techniques have successfully removed sessile polyps with accurate histological assessment^[52]. Again, the risk of bleeding and perforation exists. Immediate surgical intervention is indicated in the case of large perforations. Endoscopic closure using metallic clips or suturing is appropriate for small perforations after therapeutic endoscopic procedures^[53].

Larger sessile polyps have a greater propensity to bleed because of larger feeding vessels. Endoscopic ultrasound (EUS) would theoretically minimize the risk of bleed by visualizing the blood vessels at the base of the gastric polyp. Bardan *et al*^[54] evaluated the use of preprocedure EUS with snare polypectomy in 102 patients to minimize the risk of bleeding. However, no significant difference among bleeding rates between patients undergoing polypectomy with and without preprocedure EUS was found. A potential explanation is that bleeding after polypectomy

may originate from blood vessels undetected by the EUS technique^[54]. However, these data were not collected using more advanced EUS technologies such as newer mini probes with higher frequencies that may detect smaller vessels and better delineate submucosal margins.

Other techniques have been explored. Lo *et al*^[55] studied the proficiency of endoscopic band ligation (EBL) used to minimize bleeding risk in the removal of seventy hyperplastic polyps. Although they demonstrated the effectiveness in minimizing bleeding risks with bleeding polyps and even sessile hyperplastic polyps, this technology may have limited utility for larger polyps and gastric adenomas at risk for malignant transformation^[55]. EBL does not allow for complete resection and complete histological evaluation of these polyps. Additional electrocautery would be needed. Therefore, this technology is rarely employed. Methods such as hypertonic saline epinephrine injection, endoloops, and endoscopic hemoclips are currently utilized to control bleeding with polypectomy.

Most adenocarcinomas found within hyperplastic polyps are the differentiated type and few signet ring cell carcinoma have been reported^[56]. Data specific to gastric hyperplastic polyps and gastric cancer are not available because of limited case reports. We recommend surveillance endoscopy and EUS staging for early gastric cancer. EUS allows for imaging of the gastric wall, the degree of invasion, and regional lymph node involvement. Lymph node metastasis is present in about 10% of cases of early gastric cancer^[57]. The mainstay of treatment is gastrectomy. Newer EMR and endoscopic submucosal dissection technologies are gaining popularity in the absence of lymph node metastasis. Takekoshi *et al*^[58] reported an 85% cure rate in a series of 308 patients. The five-year survival rate was 86%, a rate similar to more aggressive surgical approaches^[58]. Hiki *et al*^[59] reported a recurrence rate of 4.2% in their series. The main disadvantage of endoscopic methods is the risk of incomplete tumor resection. Ryu *et al*^[60] investigated 344 gastric adenocarcinoma and concluded that in cancers with greater than 500 µm of submucosal invasion or a mucosal cancer larger than 3 cm, surgery should be considered because of the risk of lymph node metastasis.

Newer technologies are emerging to distinguish the histological subtype at the time of initial endoscopy. Li *et al*^[61] demonstrated the use of confocal laser endomicroscopy with upper endoscopy to characterize gastric hyperplastic polyps and adenomas. This development would obviate the need for initial biopsy and eradicate unnecessary polypectomy and associated risks. However, not all endoscopy labs have access to this technology. More accessible technologies such as magnification chromoendoscopy and narrow band imaging need larger prospective trials to prove their utility. The optimal management strategies for hyperplastic polyps have not yet been defined. As our knowledge of hyperplastic polyps continue to grow and advancements in digestive endoscopy continue to develop, our case demonstrates the current utility of diagnostic and therapeutic monopolar snare polypectomy in a symptomatic hyperplastic gastric polyp.

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Embryonal sarcoma of the liver with chondroid differentiation

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undergoing chemotherapy. This is the first report of ESL with chondroid differentiation.

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Abstract

A 31-year-old female complained of upper abdominal and back pain. Laboratory tests showed elevated levels of aspartate aminotransferase, alanine aminotransferase and α -fetoprotein. Computed tomography revealed that the tumor, measuring 14.5 cm \times 10.4 cm, occupied the anterior and medial segments of the liver and consisted of multicystic and solid lesions. The preoperative diagnosis was a hepatic cystadenocarcinoma. The operation was performed urgently because of tumor rupture. Histopathologically, spindle and asteroid cells were found to have proliferated diffusely. There were no neoplastic epithelial tumor cells. Tumor cells had periodic acid-Schiff-positive hyalin globules. At the periphery, trapped normal bile duct cells were observed. The final diagnosis was embryonal sarcoma of the liver (ESL). Interestingly, irregular islands of chondrosarcoma-like lesions were found in the tumor and the tumor-associated vascular endothelium showed immunoreactivity for KIT. Two months after the operation, the tumor recurred. At 6 mo follow-up, the patient is alive with the disease and

INTRODUCTION

Primary malignant mesenchymal tumors of the liver are rarer than epithelial neoplasms and account for no more than 2% of all primary hepatic tumors^[1]. Embryonal sarcoma of the liver (ESL) is a rare pediatric malignant tumor and only 16% of the primary hepatic sarcoma^[1]. It was first documented by Stocker and Ishak in 1978^[2]. Although more than half of patients with ESL are between 6 and 10 years of age, ESL does occur in adults. ESL has generally been considered an aggressive neoplasm with an unfavorable prognosis. However, recent reports have demonstrated that multimodal treatment of ESL can improve survival and potentially cure ESL in adults^[1,3,4]. ESL is a primitive neoplasm of mesenchymal origin. ESL tumors have frequently been defined as undifferentiated sarcoma but have also been referred to as primary sarcoma

and malignant mesenchymoma because some cases show divergent characteristics. Another tumor showing similar pathological features to ESL is anaplastic sarcoma of the kidney (ASK). Vujančić *et al.*^[5] reported 20 cases of this unusual renal neoplasm. This tumor is also composed of spindle cells proliferation with anaplastic change. A point of difference is that chondroid differentiation is seen frequently in ASK but not in ESL. In the present case, we found chondrosarcoma-like lesions in the tumor. To the best of our knowledge, this is the first report of ESL with chondroid differentiation.

CASE REPORT

A 31-year-old female was admitted to our hospital because of upper abdominal and back pain. Laboratory tests showed elevated levels of aspartate aminotransferase (AST 125 IU/L) and alanine aminotransferase (ALT 199 IU/L). Total bilirubin level was in the normal range. The level of the tumor marker α -fetoprotein (AFP) was high (42.24 ng/L) and that of carcinoembryonic antigen (CEA) was within the normal range. Abdominal computed tomography (CT) showed a huge mass measuring 14.5 cm \times 10.4 cm which occupied the anterior and medial segments of the liver. The mass consisted of multicystic and solid lesions (Figure 1A). The preoperative diagnosis was a hepatic cystadenocarcinoma. Two months after the first symptom, a bisectionectomy (liver segments IV–VIII) was urgently performed because the mass was rapidly increasing in size, measuring 16 cm \times 13 cm \times 17 cm in diameter, and bleeding. During the operation, there was a lot of hemorrhagic ascites and hematoma which came from the ruptured tumor. The tumor was soft and well-circumscribed by pseudocapsule. The tumor, inclusive of pseudocapsule, was resected. The postoperative course was uncomplicated and the patient discharged. Two months after the operation, the patient experienced back pain again. A CT scan revealed multiple metastases in the left lobe of the liver and peritoneal dissemination. Six months after the operation, the patient is alive with the disease and is undergoing chemotherapy with doxorubicin and ifosfamid.

Pathological findings

Macroscopic findings: The liver was ruptured (Figure 1B). The gross appearance of the tumor was friable and hemorrhagic. Cutting of the surface revealed a soft white mass with multilocular appearance and fibrous pseudocapsules (Figure 1C).

Microscopic findings: Upon microscopic examination, spindle-shaped cells were found to have proliferated diffusely. There were no epithelial tumor cells. Tumor cells were compactly or loosely arranged, with myxoid matrix or edema (Figure 2A). They showed marked anisonucleosis with hyperchromasia and some cells were found to be giant, multinuclear cells. Mitotic cells were abundant (19/10 high-power field). There were eosinophilic, PAS-

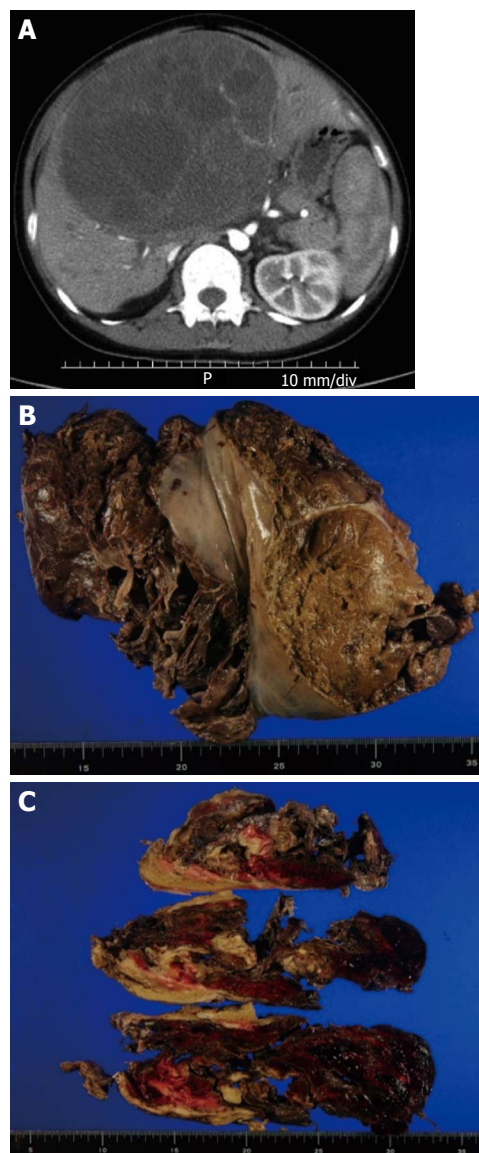


Figure 1 Computed tomography (CT) image and resected specimen. A: Abdominal CT image before surgery; B: Resected specimen. The liver was ruptured; C: Cutting of the surface revealed a soft white mass with multilocular appearance, fibrous pseudocapsules, and massive hemorrhage.

positive and diastase-resistant globules in the cytoplasm of the tumor cells (Figure 2B), stroma and apoptotic bodies. The peripheral area contained entrapped benign-appearing bile ducts which were dilated. In the focal area, we observed hyaline cartilage formation with lacunae containing irregular angular cells with one or more unusual nuclei, some of which were mitotic and resembled chondrosarcoma (Figure 2C). In some parts of this lesion, as the cartilaginous matrix was deposited around the spindle tumor cells, the tumor cells were seen to change to chondrosarcoma (Figure 2D).

Immunohistochemically, most tumor cells were strongly reactive with vimentin. Some spindle or asteroid tumor cells showed cytoplasmic positivity for desmin and smooth muscle actin (SMA), whereas tests for keratin, S100P, h-caldesmon, hepatocyte-specific antigen, AFP, HMB-45 and p53 were negative for tumor cells.

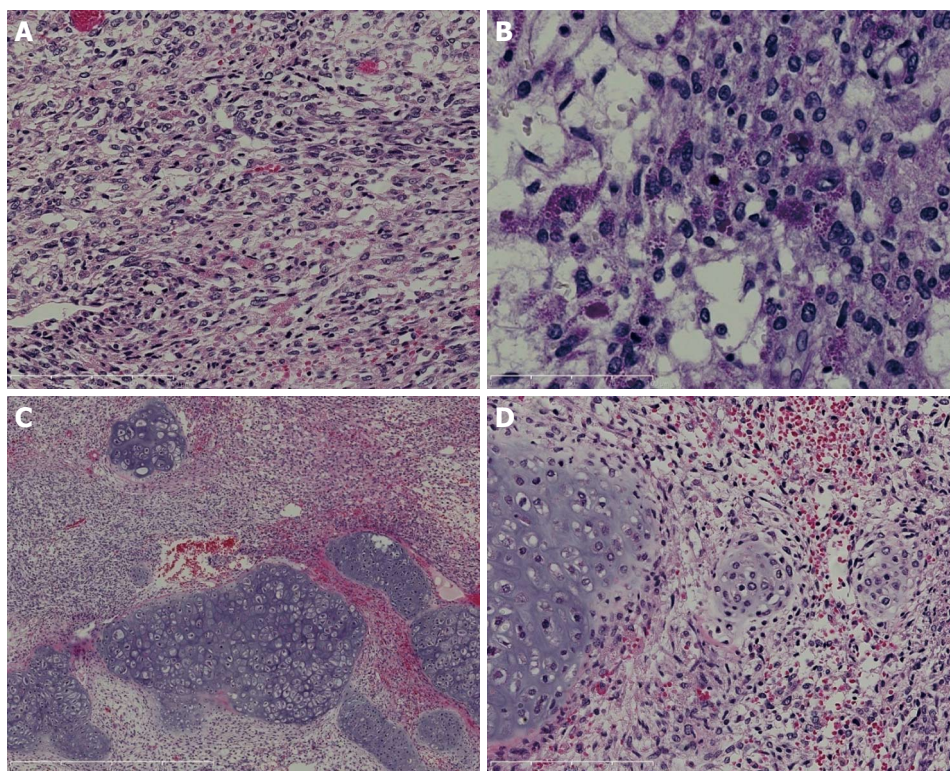


Figure 2 Histopathological findings. A: Atypical spindle cells are proliferating and are arranged compactly or loosely (HE, bar = 200 µm); B: Some tumor cells contain eosinophilic hyaline globules of various sizes, which are resistant to diastase and positive for PAS (D-PAS, bar = 100 µm); C: In a small area, cartilage formation is observed (HE, bar = 1 mm); D: The cartilage component retains a lobulated appearance. The tumor cells exhibit nuclear atypia and anisonucleosis. Some cells are mitotic. As the cartilaginous matrix was deposited around the spindle tumor cells, tumor cells were seen to change to chondrosarcoma (HE, bar = 200 µm). HE: hematoxylin and eosin stain; D-PAS: Periodic acid-Schiff stain after diastase digestion.

KIT and CD34 were not expressed in tumor cells but endothelial cells of tumor-associated vascularity expressed both KIT (Figure 3A) and CD34 (Figure 3B). The tumor was diagnosed as undifferentiated (embryonal) sarcoma of the liver. The resected margin was free of tumor infiltration.

DISCUSSION

Although several synonyms have been used in the past, ESL was clearly differentiated from other sarcomas and defined as a distinct entity by Stocker and Ishak in 1978^[2]. Usually ESL is composed of medium to large spindle or asteroid cells with marked nuclear pleomorphism. In addition, there are prominent eosinophilic, PAS-positive and diastase-resistant globules in the cytoplasm of the tumor cells.

The different diagnoses of ESL in adults include hepatocellular carcinoma, hepatoblastoma, malignant fibrous histiocytoma, leiomyosarcoma, liposarcoma, angiomyolipoma, angiosarcoma and metastasis of mesenchymal tumor, such as gastrointestinal stromal tumors (GISTs). In the present case, a chondrosarcoma-like lesion is exhibited. A mesenchymal cartilage component is also found in hepatoblastoma but there are no epithelial hepatoblastoma cells in this case.

Immunohistochemical investigation may be necessary to distinguish ESL from other sarcomas or sarcomatoid

variants of hepatocellular carcinoma. The tumor cells may be reactive to antibodies to α -1-antitrypsin^[6,7], α -1-antichymotrypsin^[3,6-8] and vimentin^[3,8]. Occasionally, tumors express desmin^[3,6,7], α -SMA^[7], muscle-specific actin^[7] and CD68^[6-8]. In some studies, tumor cells showed negative results for keratin^[4], HMB-45^[3,4,8], CD34^[3,4,8] and KIT^[4]. In the present case, ESL appears positive for SMA and desmin but negative for h-caldesmon. These results suggest that immunohistochemically some of the tumor cells in the present case show a myofibroblast phenotype.

In the present case the histopathological findings are typical, with the exception of the chondroid differentiation. Although the exact histogenesis of ESL is still unknown, it is considered that ESL may develop from multipotential mesenchymal stem cells, which have been isolated from bone marrow, adipose tissue and also from liver tissue^[9].

In our case, KIT was negative for the tumor cells as in a previous report, but we identified KIT expression in the endothelial cells within the tumor nodule. However, KIT was not expressed in endothelial cells in non-neoplastic regions.

KIT is a stem cell factor receptor and expressed during various stages of certain cell lineages, including germ cells, mast cells, stellate cells and some subsets of cerebellar neuron cells^[10]. In mesenchymal tumors, KIT expression has been reported in GISTs, seminoma and some sarcomas such as angiosarcoma and Ewing's sarcoma^[10]. There have been no reports of KIT expression in vascular endothelium

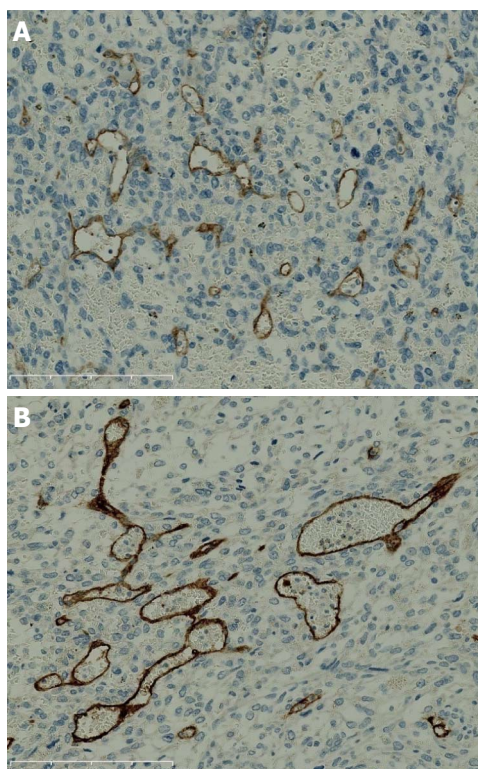


Figure 3 Immunohistochemical expression of ESL. Tests for KIT (A) and CD34 (B) gave positive results for the endothelial cells in the tumor (bar = 200 μ m). ESL; Embryonal sarcoma of the liver.

and the role of the KIT expression in tumor-associated vascularity in the present case is still unclear. However, Tallini *et al.*^[11] reported that KIT-positive cells can differentiate into smooth muscle and endothelium of the heart. KIT expression might be involved in the angiogenesis of ESL in the present case and molecular targeted drug against KIT might be effective.

In summary, we report on the first case of ESL with chondroid differentiation. The histogenesis of ESL is still unclear and further study is needed to clarify the origin of ESL.

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September 23-26, 2010
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Instructions to authors

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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer

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disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorfeide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/EID/eid.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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